

Mastocytosis

The Great Masquerader

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Abstract

Variants of mastocytosis can present with puzzling cutaneous and systemic symptoms and signs that can result in an erroneous diagnosis of idiopathic urticaria or idiopathic anaphylaxis. The molecular basis of mastocytosis is now better understood, with updated classification based on distinct growth factor and oncogene abnormalities. Elicitation of a full history and careful attention to the skin examination will usually provide the clinician enough information to deduce that the condition is not simply chronic idiopathic urticaria.

Index Entries

Mast cell; tryptase; drug allergy; *c-kit* gene mutation; urticaria pigmentosa.

Case 1

A 32-yr-old woman reported 3 yr of recurrent urticaria on her abdomen and thighs, occurring approximately twice a week. She was diagnosed with chronic urticaria (CU) and took diphenhydramine as needed for outbreaks, which was effective. Hot showers, tight clothing, and sunbathing triggered the devel-

opment of hives. She noted that in the past 6 mo, there were faint erythematous "freckles" present on her abdomen and thighs that did not resolve. On exam, numerous faintly erythematous 1- to 2-mm macules were present on her lower abdomen, sacrum, and inner thighs. A skin biopsy confirmed a diagnosis of the telangiectasia macularis eruptive perstans variant of mastocytosis. A serum tryptase was 3.3 ng/mL.

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Case 2

A 55-yr-old male with a history of irritable bowel syndrome presented with a history of facial flushing, syncope, and hypotension after taking penicillin for 1 wk when he was in his 40s. He was given intravenous fluids in the emergency department and diagnosed with penicillin allergy. Two years later, he again developed flushing with syncope. Once more he visited the emergency department and received intravenous fluids. He vaguely remembered taking ibuprofen at the time. He was therefore told to avoid ibuprofen. At age 55 yr, he took ibuprofen for wrist pain and shortly thereafter developed facial flushing without syncope or hypotension. In the emergency department, he was given intravenous diphenhydramine, which resulted in the immediate resolution of his flushing and erythema. He was referred for evaluation of multiple adverse drug reactions.

As part of the investigation, a random serum tryptase level was drawn, which was greater than 200 ng/mL.

Mast Cells: Biology

Mast cells are hematopoietic cells of a distinct myeloid lineage. They are long-lived in vascular tissues with a lifespan of several months. Mast cells are formed in the bone marrow and mature after reaching their final destination at portals of entry to noxious or foreign substances, such as skin and mucosal surfaces. Despite the presence of similar metachromatic granules in both mast cells and basophils, mast cells are not basophils in tissues, nor do they share the same lineage. Mast cells are characterized by surface markers, such as FcεR1, CD13, CD34, CD68, and CD117 (KIT). They contain metachromatic granules containing preformed vasoactive and immunoregulatory mediators. These include the prototypical histamine, heparin, chymase, and tryptase. Aside from these preformed peptides, mast cells also secrete newly formed lipid and protein mediators upon activation by T-cells. These include

the lipid-derived arachadonic acid derivatives, such as prostaglandin (PGD)₂ and leukotriene (LTC)₄. Activated mast cells also produce interleukin (IL)-1, IL-6, IL-13, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and possibly other cytokines that are incompletely characterized, such as stem cell factor (SCF). T-cells and mast cells putatively secrete SCF. SCF binds KIT, a tyrosine kinase receptor that initiates a secondary signaling cascade, which ultimately leads to activation of mast cells and their differentiation (1,2).

In humans, mast cells are subdivided between tryptase-positive mast cell (MCt) and tryptase- and chymase-positive mast cell (MCtc) subtypes based on neutral protease composition. MCts produce tryptase only, whereas MCtcs produce chymase, carboxypeptidase, and cathepsin in addition to tryptase (3). Activation of MCt in vitro is primarily limited to stimulation with anti-immunoglobulin (Ig)E and calcium ionophore A23187, whereas MCtc also degranulates upon exposure to compound 48/80, basic polypeptides, morphine sulfate, formyl-methionyl-leucyl-phenylalanine peptides, substance P, and anaphylatoxin C5a (4).

The exact teleological purpose of mast cells has proven elusive over the years. Aside from the well-known opsonin binding of mast cells to parasitic helminthes via IgE, the immunological purpose of mast cells is not fully understood. However, strides have been made in recent years. In the murine model, there is an increase in mortality in mast cell-deficient mice with bacterial peritonitis (5). In addition, mast cells have been demonstrated to synthesize mRNA encoding TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-5, IL-13, and LTC₄ in response to lipopolysaccharide and peptidoglycan stimulation of Toll-like receptors (TLR) 1, 2, 4, and 6 of mast cells (6). More recently, double-stranded RNA and viruses have been shown to induce type I interferon (IFN) production in mast cells via TLR-3 (7). Ongoing and future studies may ultimately prove a pivotal role for mast cells in innate im-

munity, in addition to their known role in acquired immunity in parasitic infections (8). The pathological role of mast cells in allergic disease may therefore simply be a protective response gone awry. One of these awry states is mastocytosis.

Mastocytosis

Mastocytosis is a rare myeloid clonal disorder of mast cells. Historically, mastocytosis had been classified as either cutaneous limited or systemic (9). Despite recent insight into the pathophysiology of mastocytosis, this clinical classification is still applicable today. This is because mast cell proliferation limited to cutaneous tissues carries a highly favorable clinical prognosis.

Cutaneous Mastocytosis

Cutaneous mastocytosis is predominately a pediatric illness usually presenting in patients less than 6 mo of age. In many children, the condition spontaneously remits before the age of 2 yr and remits in most by puberty (10). However, urticaria pigmentosa and telangiectasia macularis eruptive perstans may also present in adults, often with intervals of many years between onset and diagnosis. Cutaneous mastocytosis is loosely classified into four subclasses based on the prototypical skin lesions seen.

1. Urticaria pigmentosa are commonly 0.5-cm red-brown macules or papules characterized by the presence of more than 10 times the number of mast cells compared to normal skin (11–13). The lesions exhibit Darier's sign (i.e., the development of a wheal and flare when the lesions are rubbed or scratched).
2. Diffuse cutaneous mastocytosis is often thought of as a confluence of urticaria pigmentosa (14–16).
3. Mastocytomas are benign, solid, cutaneous mast cell tumors (17).
4. Telangiectasia macularis eruptive perstans is a form of cutaneous mastocytosis with telangiectatic macules exhibiting Darier's sign (18).

Systemic Mastocytosis

In recent years, the pathophysiology of mastocytosis has been better elucidated. This has led to both new diagnostic and classification schemes by the World Health Organization (WHO) as depicted in Table 1 (19,20). Unlike cutaneous mastocytosis, systemic mastocytosis often presents during adult life; however, skin manifestations of cutaneous mastocytosis may be the only symptoms and signs for many years. As the name implies, systemic mastocytosis differs from cutaneous mastocytosis in the involvement of disease in a tissue other than skin. Periodic degranulation of mast cells with resultant release of vasoactive and immunoregulatory substances is believed to be responsible for the symptoms seen in systemic mastocytosis. These include episodic flushing, itching, headache, dyspepsia, diarrhea, abdominal pain, musculoskeletal pain, syncope, tachycardia, and hypotension, hypertension, and neuropsychiatric symptoms.

Diagnosis

Common tissues of involvement are bone marrow, spleen, liver, lymph nodes, and the gastrointestinal tract. Because the bone marrow is almost always involved and no comparative information is available for the evaluation of pathological mast cells in non-bone marrow tissues, bone marrow biopsy and aspirate often provide the tissue diagnosis of choice for the evaluation for systemic mastocytosis (21). Multifocal, dense infiltrates of mast cells (15 mast cells found aggregating together) in the bone marrow or other noncutaneous tissues is the major criteria under the WHO diagnostic criteria. Abnormal spindle-shaped morphology in more than 25% of all mast cells seen in the bone marrow or noncutaneous tissue is one of four minor criteria.

Prior to any invasive evaluation, a simple serum tryptase level may be a good screening test, especially in the adult populations. The use of tryptase as a surrogate marker for mast cell burden is possible owing to the constitu-

Table 1
World Health Organization Diagnostic Criteria for Systemic Mastocytosis and Subclassifications

Systemic mastocytosis (SM) (manifestation in an organ other than skin with either one major criterion and one minor criterion or three minor criteria).

Major criterion

1. Bone marrow or extracutaneous biopsy with multifocal, dense, infiltration of mast cells (MCs; >15 MCs in aggregates).

Minor criteria

1. Serum tryptase >20 ng/mL (does not count in AHNMD).
2. Greater than 25% of MCs spindle-shaped or atypical morphology on BM smear or tissue Bx.
3. Evidence of CD2 and/or CD25 on MCs in BM, blood, or tissue
4. Codon 816 c-kit point mutation in blood, BM, or extracutaneous tissue.

SM with BM <20% MCs

Indolent systemic mastocytosis (ISM) without B or C findings

1. Smoldering with two or more B findings.
2. Variable prognosis.
3. Isolated BM mastocytosis (no skin findings and tryptase <30).
4. Good prognosis.

Aggressive SM or ISM with C findings

1. Lymphadeopathic SM with eosinophilia.
2. Poor prognosis.

SM with an AHNMD prognosis and Rx based on AHNMD

1. SM-AML (>20% myeloblasts).
2. SM-MDS (dysplasia)
3. SM-MPD (PRV, ET, CML, CLL).
4. SM-HES (eosinophilia and FIPL1/PDGF α).
5. SM-CMML (>1000 mono and dysplasia).
6. SM-NHL.

SM with BM >20% MCs

Mast cell leukemia (MCL)

1. Peripheral blood $\geq$ 10% MCs.
2. Poor prognosis <1 yr.

Aleukemic MCL

1. Peripheral blood <10% MCs.

MC sarcoma (three known cases)

1. Grave prognosis.

B-Findings—high MC burden and expansion of defect into other myeloid lineage

1. Greater than 30% infiltration grade MC in BM and serum tryptase <200 ng/mL.
2. Hypercellular marrow with loss of fat cells, discrete signs of dysmyelopoiesis without significant cytopenia, or WHO criteria for MDS or MPD.
3. Organomegaly: palpable HSM or LAD (<2 cm on CT or US) without organ dysfunction.

C-Findings—impaired organ function owing to MC infiltration via Bx

1. Cytopenia: ANC <1000/ μ L, Hb <10 g/dL, or Plt <100 K/ μ L.
2. Hepatomegaly with ascites and impaired liver function.
3. Palpable splenomegaly with hypersplenism.
4. Malabsorption with hypoalbuminemia and weight loss.
5. Skeletal lesions: large-sized osteolytes and/or severe osteoporosis causing pathological Fx.
6. Life-threatening organopathy in other organs caused by neoplastic MC on Bx.

Adapted from refs. 19 and 20.

MC, mast cells; BM, bone marrow; AHNMD, associated clonal hematological non-mast cell lineage disease; SM, systemic mastocytosis; AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disorder; PRV, polycythemia rubra vera; ET, essential thrombocytosis; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; HES, hypereosinophilic syndrome; CMML, chronic monocytic myelogenous leukemia; NHL, non-Hodgkin's lymphoma; CT, computed tomography; US, ultrasound; Hb, hemoglobin; Bx, biopsy; Fx, fracture; ANC, absolute neutrophil count; Plt, platelet; LAD, lymphadenopathy; HSM, hepatosplenomegaly.

tive nature of tryptase in mast cells (22). It should be noted, however, that other disease states may be associated with elevated tryptase levels, such as myeloid neoplasms and severe allergic reactions (23–26). Therefore, serum tryptase greater than 20 ng/mL only satisfies one of the WHO's minor criteria if an associated hematological non-mast cell lineage disease (AHNMD) has been excluded. This, of course, would have been ruled out with examination of the bone marrow as stated earlier.

Unlike normal mast cells, mast cells in systemic mastocytosis are often fusiform (27). In addition to surface markers found on normal mast cells, mast cells in systemic mastocytosis often, but not always, express CD2 and CD25, which are other minor criteria for systemic mastocytosis (28).

Lastly, the presence of a *c-kit* mutation completes the four minor criteria for systemic mastocytosis. As previously mentioned, KIT is a tyrosine kinase receptor for SCF, which promotes mast cell differentiation and growth. This receptor is encoded by the gene *c-kit*. A single-point mutation of *c-kit* at codon 816 from asparagine to valine leads to ligand-independent phosphorylation of KIT. Thus, this point mutation leads to unregulated mast cell differentiation and growth. Indeed, a codon Asp816Val *c-kit* mutation is found in 80% of mastocytosis cells and is the most common mutation in *c-kit* in this disease (29,30). Several other mutations have been identified, especially in patients with an AHNMD (31). These are among other genetic defects and polymorphisms believed to contribute to the pathogenesis of systemic mastocytosis.

One other genetic defect worth mentioning is the presence of a FIP1-like-1 (*FIPL1*)/platelet-derived growth factor receptor α (*PDGFR α*) fusion gene defect. Although it is not formally part of the WHO classification scheme, its presence has therapeutic implications. In a subset of patients with systemic mastocytosis with associated eosinophilia who express the *FIPL1*/*PDGFR α* fusion gene product appear to

respond to imatinib mesylate, a tyrosine kinase inhibitor already in use for chronic myeloid leukemia. Imatinib mesylate has activity against bcr-abl, KIT, and PDGFR tyrosine kinases (32–35). Unfortunately, in vitro studies with imatinib mesylate have demonstrated cytotoxic effects on wild-type KIT, but not on KIT with codon Asp816Val mutation (36). Given that 80% of mastocytosis cells demonstrate this mutation, imatinib mesylate is not expected to be beneficial for the majority of mastocytosis cases. Even mutations other than Asp816Val, such as *c-kit* mutation Phe522Cys, have variable response to imatinib in case studies (37,38).

Classification

After the diagnosis of systemic mastocytosis is made with either one major and one minor criterion or three minor criteria, systemic mastocytosis can be classified into one of five major classifications: indolent systemic mastocytosis, systemic mastocytosis with AHNMD, aggressive systemic mastocytosis, mast cell leukemia, and mast cell sarcoma (Table 1). Each one of these has subclassifications as outlined in Tables 1 and 2. Of these, indolent systemic mastocytosis and its respective subclasses is the most common, and accounts for upward of 80% of cases. Overall, they have good prognosis and a normal life expectancy. On the other hand (39), systemic mastocytosis with AHNMD share a prognosis similar to the non-mast cell hematological disease. Aggressive systemic mastocytosis has a worse prognosis. IFN- α -2b has been studied in a phase II multicenter trial in aggressive systemic mastocytosis, but only about one-third of patients responded (40). Mast cell leukemia is the rarest of all forms and also carries the worst prognosis, with only few months of survival with or without treatment (41).

Treatment

Avoidance of triggers is a reasonable initial approach for a patient with cutaneous and systemic mastocytosis. Potential triggering factors

Table 2
Mediators and Corresponding Symptoms in Systemic Mastocytosis

I. Systemic	
• Vascular instability	Histamine, LTC ₄ , LTE ₄ , PGD ₂ , PAF, endothelin
• Increased vasopermeability	Histamine, LTC ₄ , LTD ₄ , PAF
• Fibrosis	Transforming growth factor- β
• Eosinophilia	IL-5
• Lymphocytic infiltrations	IL-16, lymphotaxin
• Local anticoagulation	Heparin
• Mast cell hyperplasia	IL-3, IL-6, SCF
• Cachexia	Tumor necrosis factor- α , IL-6
II. Skin	
• Pruritus	Histamine
• Urticaria	Histamine, LTC ₄ , PAF
III. GI tract	
• Gastric hypersecretion	Histamine
• Cramping, abdominal pain	Histamine, LTC ₄ , PAF
IV. Lungs	
• Bronchoconstriction	Histamine, PGD ₂ , LTC ₄ , LTD ₄ , PAF, endothelin
• Secretion of mucus	Histamine, proteases, PGD ₂ , LTC ₄
• Pulmonary edema	Histamine, LTC ₄ , PAF
V. Skeletal system	
• Bone remodeling	Tryptase, chymotryptic proteases, IL-6
• Osteoporosis	Heparin

Adapted from ref. 42.

IL, interleukin; LT, leukotriene PG, prostaglandin; PAF, platelet-activating factor.

may be physical, such as heat, cold, pressure, sunlight, or exercise. Certain drugs are known to cause nonimmune-mediated mast cell degranulation, such as aspirin, nonsteroidal anti-inflammatory drugs, alcohol, opiates and their derivatives, radiographic dyes, and general anesthesia/muscle relaxants (specifically succinylcholine, D-tubocurarine, gallamine, and decamethonium). Venoms of snakes and insects, polymers (such as dextran and gelatin), and biologicals (such as IFN- α) are other miscellaneous potential triggers for patients. Triggers to avoid must be individually tailored on a case-by-case basis (42).

Most forms of cutaneous mastocytosis spontaneously remit among children by puberty. Therapy is therefore aimed at reducing pruritis associated with the lesions and the social stigma associated with skin lesions. One specific therapy worthy of mention in this circumstance is oral methoxypsoralen along with long-wave ultra-

violet A (PUVA). Light therapy has been demonstrated to provide some success in patients with cutaneous mastocytosis. This therapy reduces the number of mast cells and their mediators in the skin with resulting in a reduction in pruritis, in addition to a decrease in wheal and flare formation (43–45).

Because no cure exists for systemic mastocytosis, the aim of therapy is to reduce the symptoms induced by effectors release by mast cells. Table 2 summarizes various approaches (42). As most of the skin, gastrointestinal, pulmonary, and bone symptoms are mediated via histamine, antihistamines are logically the mainstay of therapy. To date, four different histamine receptors (H1–H4) have been described and cloned. H1 and H2 receptor blockers are commercially available in the United States, whereas H3 and H4 blockers are not yet available for clinical use (46). H1 receptors blockers primarily inhibit effectors on blood vessels

and bronchial and intestinal smooth muscle. H2 receptor blockers primarily block gastrointestinal side effects. Symptoms of most patients are controlled with these measures alone. Their side effects are mostly limited to the sedative nature of older antihistamine. With the availability of nonsedating antihistamines, including loratadine, fexofenadine, and cetirizine, treatment of systemic mastocytosis has become more tolerable. However, histamine is only one of the mediators released. Cromolyn sodium and ketotifen are inhibitors of mast cell degranulation. Use of cromolyn sodium and ketotifen (which is not available in the United States) provides additional relief to patients, especially those with gastrointestinal symptoms (47,48). The only drawback to their use is the frequency of dosing required.

The treatment of the systemic mastocytosis with AHNMD is dependent on the non-mast cell portion of the disease. The treatment is therefore complex and beyond the scope of this brief review. It is interesting to note that even with polychemotherapeutic approaches, only the associated hematological non-mast cell lineage disease achieves remission, whereas mastocytosis persists in these patients (49). Patients with systemic mastocytosis with AHNMD should be referred to a hematologist/oncologist for definitive treatment. As alluded to earlier, imatinib has a special indication in the treatment of systemic mastocytosis with associated eosinophilia and presence of the *FIPL1/PDGFR α* fusion gene product (32–35). IFN had been used with limited success in aggressive systemic mastocytosis.

Although blocking of mediators of disease is still the mainstay of therapy, efforts have been made to specifically target the underlying pathogenesis of systemic mastocytosis, particularly toward deactivating the unregulated KIT ligand in this disease. Recently, a group in Munich, Germany reports the use of AMN107, a novel tyrosine kinase inhibitor, to reduce the growth of c-kit D816V-harboring murine cells not otherwise inhibited by imatinib

(50). Hopefully, further research in laboratory science will soon translate to clinical applications in the near future.

Returning to the Cases

The woman in Case 1 represents a patient who was diagnosed with CU when she really had a variant of mastocytosis. She has subsequently been placed on daily nonsedating H1 and H2 blockers without recurrence of symptomatic urticaria. She was also given self-injectable epinephrine and counseled that sometimes certain triggers may result in massive activation of mast cells with generalized flushing and hypotension. She was informed of common triggers and advised to obtain a medical identification bracelet. Aside from flushing, the patient described in Case 2 did not have urticaria pigmentosa or other prototypical skin lesions found in mastocytosis. As mentioned, his laboratory work-up revealed a serum tryptase higher than 200 ng/mL on two separate occasions. Neither CD2 nor CD25 were found by fluorescence-activated cell sorter on flow cytometry. Although his *c-kit* mutation analysis was normal, his bone marrow biopsy did show elevated levels of monomorphic spindled mast cells. They were both diffuse and paratrabecular with faint granular cytoplasm and comprised 12.5% of the marrow differential. He was given the diagnosis of indolent systemic mastocytosis and a subclassification of smoldering systemic mastocytosis because of the heavy mast cell burden, as suggested by a greater than 200 ng/mL tryptase on multiple occasions, discrete signs of dysmelopoiesis on bone marrow biopsy, and splenomegaly and lymphadenopathy on computed tomography. He was started on oral H1 and H2 antihistamines, and provided with self-injectable epinephrine, advice on triggers and medical identification bracelet information. He continues to be monitored serially for possible transformation of his systemic mastocytosis. In retrospect, the temporal relationship between

his flushing and ibuprofen intake was a diagnostic clue. It is likely that his previously diagnosed irritable bowel syndrome is yet another manifestation of mast cell mediators. Atypical drug reactions should raise suspicion for alternative diagnosis as with this case of smoldering systemic mastocytosis.

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