

Systemic Mastocytosis: Clinical Manifestations and Differential Diagnosis

Joseph H. Butterfield, MD^{a,b,*}

^a*Division of Allergic Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA*

^b*Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA*

The rarity of systemic mastocytosis (SM) and the fact that many of its recognized symptoms are shared by other more common disorders serve to delay or hinder its diagnosis. Although SM is discovered serendipitously in some cases, patients with SM usually present to their physicians for evaluation of one or more symptoms that have developed insidiously, suddenly, or recurrently. These symptoms can be life-threatening or cause great physical and emotional distress. The diagnosis of SM may require the clinician to “think outside the box” when faced with a patient who has common symptoms that defy explanation after testing for the “usual suspects.”

Mast cells are heterogeneous in their cytokine [1] and neutral protease content [2] and in their response to secretagogues, such as substance P, compound 48/80, C5a, formyl-met-leu-phe (FMLP), and morphine [3–10]. For example, cutaneous mast cells, but not pulmonary, intestinal, or cardiac mast cells release significant amounts of histamine when exposed to morphine, whereas mast cells from each one of these tissues respond to anti-IgE [10]. In contrast to rat peritoneal mast cells, histamine release by human intestinal and lung mast cells is not inhibited by disodium cromoglycate, whereas histamine release by mast cells from all these sites is inhibited by theophylline [7]. Likewise, patients with SM may have considerable variation in their presenting and subsequent symptoms and in their response to treatment. This review includes common and uncommon symptom presentations for SM and examines how to distinguish SM from other disorders that often can be caused by excessive sporadic systemic release of mediators.

* Correspondence. Division of Allergic Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

E-mail address: butterfield.joseph@mayo.edu

Systemic mastocytosis

SM results from uncontrolled proliferation of tissue mast cells and the release of mast cell–derived mediators [11]. One of the difficulties with diagnosing SM is its low incidence, estimated at 0.000667%, compared with that of other disorders whose symptoms overlap those commonly found in SM [12,13]. Mast cells are powerhouses for the generation of preformed mediators, such as histamine, eosinophil chemotactic factors of anaphylaxis, neutrophil chemotactic factor, and heparin as well as enzymes like tryptase, chymase, peroxidase, superoxide dismutase, β -glucuronidase, hexosaminidase, and arylsulfatase, which are responsible for many of the symptoms of SM. Mast cells also produce newly formed mediators, including products of the cyclooxygenase (12-L-hydroxy-5,8,10-heptadecatrienoic acid [HHT], prostaglandin D₂) and lipoxygenase (hydroxyeicosatetraenoic acid [HETE], leukotriene [LT] C₄, LTD₄, LTE₄) pathways [13] as well as multiple chemokines [14], interleukins, and platelet-activating factor [15]. Degranulation of mast cells with subsequent clinical symptoms can be triggered not only by IgE but also by physical (eg, rubbing, physical exertion, extreme temperatures, sunlight), chemical (eg, alcohol, general anesthetics, nonsteroidal anti-inflammatory drugs, polymyxin B, dextran, radiologic contrast media), or biologic (eg, animal venoms, stings from insects or jellyfish, bacterial proteins) agents [16]. Often, however, the trigger for degranulation in SM is not evident.

Mast cells are long-lived cells [17,18] that reside in vascularized tissues close to blood vessels and nerves [18,19]. They are thus located in ideal positions for rapid delivery of their mediators to the circulation, with resultant overwhelming clinical symptoms. Mast cells are also intimately related to sensory nerves, and mast cell–nerve interactions are well known. Histamine release by cutaneous mast cells can be stimulated by substance P, vasoactive intestinal peptide, and somatostatin [8,20–22].

Clinical manifestations of SM can be ascribed to the local or remote effects of mast cell–generated mediators, such as histamine’s known effects on the smooth muscle of the cardiovascular and gastrointestinal systems (facial flushing, tachycardia, hypotension, headache, nausea, vomiting, diarrhea) [23] and to the presence of excessive numbers of mast cells that impair the normal function of organs. The World Health Organization classification of mastocytosis includes mastocytosis restricted to the skin and the following systemic variants: indolent SM, SM associated with a clonal hematologic non-mast-cell lineage disease (SM-AHNMD), aggressive SM, and mast cell leukemia [24]. Symptoms related to mast cell mediator release are common in indolent SM, which accounts for most of the cases of SM. In patients with SM-AHNMD, it may be difficult to distinguish symptoms attributable to mastocytosis from those attributable to the associated (usually myeloid) hematologic disorder, and treatment must be directed separately at each disorder. In aggressive SM and mast cell leukemia, compromised organ function attributable to mast cell infiltration results

in different symptoms, such as malabsorption and weight loss, osteolyses, hypersplenism, and others [25]. These symptoms have been called “C-findings” by consensus classification [26]. Serum tryptase levels also have been useful for estimating the burden of mast cells in patients with SM [27]. Episodic symptoms of mediator release are, in our experience, a frequent presentation for patients with SM. Mast cell mediator levels in samples of serum (tryptase) and urine (eg, n^+ methylhistamine, 11β prostaglandin $F_{2\alpha}$) obtained when patients with SM are asymptomatic may be increased but also may be normal. Therefore, it may be necessary to obtain samples contemporaneously with the onset of symptoms to detect inappropriately increased mediator levels. Unfortunately, obtaining these samples is often difficult or impossible when a patient is seen in an acute care or emergency room setting, where time is scarce and knowledge of SM is scant.

“No symptoms”

A subset of patients with SM does not present with symptoms characteristic of mast cell degranulation and mediator release. Rather, mastocytosis is discovered incidentally in the course of evaluation of another disorder(s). Examples of such veiled cases include discovery of SM in a patient with osteoporosis [28,29]; during the workup of a patient with eosinophilia [30,31], thrombocythemia [32], or solid tumors [33]; and during evaluation of any of the various leukemias with which SM has been associated [34–37]. In one series [38], 2 of 40 patients were asymptomatic at the time SM was discovered incidentally on review of a bone marrow biopsy for neutropenia in the first patient and anemia in the other patient.

Constitutional symptoms, including weakness [39], lethargy, night sweats, and weight loss [40], may be presenting symptoms of aggressive or rapidly progressive SM or SM-AHNMD. Plasma interleukin-6 levels correlate with the severity of bone marrow abnormality, organomegaly, and extent of skin involvement [41]. If skin findings of SM are overlooked or subtle, these nonspecific symptoms may lead to a search for more common disorders, such as thyroid disease, vasculitis, neurologic disorders, tuberculosis, carcinoma, or blood dyscrasias.

Anaphylaxis and spells

One of the most common presenting complaints of patients is “spells” during which the sudden onset of symptoms recurs in a self-limited stereotypic fashion. Spell symptoms may result from endocrine, cardiovascular, psychologic, pharmacologic, neurologic, and miscellaneous causes [42]. As illustrated in [Box 1](#), a wide net may need to be cast to evaluate any patient completely for spells.

Box 1. Differential diagnosis of spells**Endocrine**

- Pheochromocytoma
- Thyrotoxicosis
- Primary hypogonadism (eg, menopausal syndrome)
- Medullary thyroid carcinoma
- Pancreatic tumors (eg, insulinoma)
- Hypoglycemia
- Carbohydrate intolerance
- "Hyperadrenergic spells"

Cardiovascular

- Labile essential hypertension
- Cardiovascular deconditioning
- Pulmonary edema
- Syncope
- Orthostatic hypotension
- Baroreflex dysfunction
- Paroxysmal cardiac arrhythmia
- Angina
- Renovascular disease

Psychologic

- Anxiety and panic attacks
- Somatization disorder
- Hyperventilation

Pharmacologic

- Withdrawal of adrenergic inhibitor
- Monoamine oxidase inhibitor treatment and tyramine (in foods) or sympathomimetic drugs
- Sympathomimetic ingestion
- Illegal drug ingestion (eg, cocaine, phencyclidine hydrochloride [PCP], lysergic acid diethylamide [LSD])
- Chlorpropamide-alcohol flush
- Vancomycin ("red man syndrome")

Neurologic

- Postural orthostatic tachycardia syndrome
- Autonomic neuropathy
- Migraine headache
- Seizure disorders
- Diencephalic epilepsy (autonomic seizures)

Fatal familial insomnia
Stroke
Cerebrovascular insufficiency

Other

Mastocytosis: systemic or activation disorder
Environmental allergies
Carcinoid syndrome
Recurrent idiopathic anaphylaxis
Unexplained flushing spells
Polycythemia vera
POEMS syndrome (polyneuropathy, organomegaly,
endocrinopathy, M protein, and skin changes)

From Young WF Jr, Maddox DE. Spells: in search of a cause. Mayo Clin Proc 1995;70:758.

In SM, the sudden explosive release of mast cell mediators simultaneously affects many organ systems and may give the outward appearance of anaphylaxis [43,44]. The release of mediators in a compressed time frame results in many of the multiple signs and symptoms that patients with SM can experience chronically. Commonly, anaphylaxis symptoms of hemodynamic collapse, urticaria and angioedema, pruritus, nausea, vomiting, diarrhea, shortness of breath, dysphonia, cardiac arrhythmias, impaired level of consciousness, headache, uterine cramps or bleeding, a sensation of impending doom, and flushing singly or in various combinations [45] may lead patients to seek medical evaluation.

Although there is no reported increase in the prevalence of atopic disease in patients with urticaria pigmentosa [46], it is not difficult to understand why many patients with SM are first evaluated for anaphylaxis. In the series of patients with SM reported by Travis and colleagues [11], anaphylactic symptoms were precipitated by exposure to specific triggers, such as medications (penicillin, aspirin, narcotic analgesics, sulfonamide, procaine, and pentazocine), exposure to heat or cold, foods (chocolate and salted nuts), rubbing of the skin, alcohol, or stress.

Therefore, the various types of anaphylaxis that have been defined [47–50] must be kept in mind and distinguished from SM. These anaphylaxis subgroups include allergic anaphylaxis caused by IgE antibody-mediated mast cell and basophil degranulation; anaphylactoid reactions caused by external agents, such as radiocontrast media, mannitol [51], or fluorescein [52], that trigger non-IgE-mediated degranulation of mast cells and basophils; exercise-induced anaphylaxis, a distinct type of physical allergy frequently associated with other forms of physical allergies, such as cold and cholinergic

urticaria [53]; food-dependent exercise-induced anaphylaxis [54,55]; and idiopathic anaphylaxis, a syndrome that has no identifiable triggers and may constitute nearly 40% of reported cases of anaphylaxis [56].

Documentation of excessive mediator release can be crucial for making a definitive diagnosis of spells like those caused by pheochromocytoma, by carcinoid syndrome, or by SM. Numerous drugs and foods can spuriously affect urine mediator values. For example, in the diagnosis of pheochromocytoma, a disorder caused by catecholamine-producing tumors of the sympathetic nervous system, false increases of urinary metanephrine and catecholamine levels may result from ingestion of tricyclic antidepressants, amphetamines, or methyl dopa. In the diagnosis of carcinoid syndrome, false increases of 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) levels may be caused by foods (kiwis, plums, avocados, pineapples, bananas, walnuts, hickory nuts, pecans) ingested within 3 days of sample collection or by drugs (guaifenesin, acetaminophen) [42]. False-negative urinary mediator results for the detection of pheochromocytoma may occur from metyrosine or methylglucamine use; likewise, aspirin, levodopa, and phenothiazine use may falsely lower urinary 5-HIAA determinations [42].

Of all the symptoms attributed to spells, perhaps the most common complaint is flushing. Flushing, commonly visible on the face, upper trunk, and arms, is a normal physiologic thermoregulatory response to hyperthermia [42], resulting in redness of the skin and warmth. It is useful to distinguish neurogenic “wet” flushing from direct vasodilatory flushing. Wet flushing is caused by sympathetic cholinergic neuron discharge that stimulates vasodilation of cutaneous blood vessels and triggers sweat glands in the skin [57,58]. “Dry” flushing is caused by vasoactive chemical mediators, such as histamine, kinins, and prostaglandins, and is not associated with perspiration [42].

As with other symptoms commonly attributed to SM, flushing itself has a myriad of potential triggers. Patients with idiopathic flushing are commonly women with a long duration of symptoms, normal results of laboratory evaluations, and, in a high percentage, somatization disorder [59]. Flushing also may occur as a physiologic response to embarrassment or anger or as a side effect of drugs (glyceryl trinitrate, prostacyclin, nicotinic acid, phentolamine, nifedipine), alcohol, foods (gustatory flushing), or spices (monosodium glutamate) [60]. The flushing in Asian racial groups after alcohol ingestion occurs as a consequence of low K_m aldehyde dehydrogenase, resulting in increased plasma acetaldehyde levels [61].

Flushing and other symptoms from gastrointestinal carcinoid tumors develop after metastasis of the tumor to the liver [62,63]. Carcinoid flushing is generally widespread, patchy, violaceous, and evanescent, lasting only a few minutes and is uncommonly associated with hemodynamic changes. Carcinoid syndrome can be distinguished from SM by its response to the long-acting somatostatin analogue octreotide, its specific pattern of mediator excretion, and the aggravation of carcinoid flushing by epinephrine administration [64]. Levels of urinary 5-HIAA, the principal metabolite of

serotonin, are increased to greater than 150 μmol per 24 hours in patients with carcinoid syndrome [60]. In contrast, flushing in patients with SM is bright red, pruritic, and burning and may be accompanied by symptoms attributable to mast cell mediator degranulation, such as headache, lacrimation, wheezing, abdominal colic, and diarrhea [60,63].

Because of the rarity of gastric carcinoid tumor and SM, confusion may arise in differentiating the flushing of one from that of the other, particularly because the appearance of the flush is similar, both are associated with increased urinary histamine metabolites [65,66], and the presence of histamine-related symptoms may accompany the flush in both. Although patients with gastric carcinoid tumors also have increased serum levels of chromogranin A [66], endoscopic examination and biopsy of suspect lesions may be necessary to confirm the diagnosis of gastric carcinoid. Flushing from gastric carcinoid often occurs postprandially. SM may be distinguished by bone marrow findings; other cutaneous signs, such as the presence of urticaria pigmentosa or Darier sign; and the presence of other mediators, such as serum tryptase [67,68] and urinary prostaglandins [69], that are absent in carcinoid syndrome (Table 1).

Cardiovascular symptoms

Persistent cardiovascular symptoms, despite standard therapy, are often overlooked as manifestations of SM. In the patient described here, SM was discovered only after a prolonged trial of aggressive but ineffectual cardiovascular treatments, including pacemaker placement.

A 66-year-old woman was evaluated at our clinic for a 7-year history of palpitations, hypotension, flushing, loss of consciousness, diarrhea, and incontinence. Neurologic evaluation was normal. Because of resistance of her symptoms to cardiovascular medications, she had previously undergone radiofrequency catheter ablation of the atrioventricular node and dual-chamber pacemaker placement. The day after the pacemaker implantation, she had a typical hypotensive spell accompanied by nausea and flushing. Subsequent evaluation showed perivascular aggregates of mast cells in the bone marrow consistent with mastocytosis. Treatment with doxepin and aspirin prevented recurrence of her symptoms.

Cardiovascular findings commonly accompany other presenting symptoms of SM, especially during anaphylactic episodes. As isolated signs, however, cardiovascular symptoms, such as tachycardia, chest pain, hypertension, hypotension [11], and syncope, are often overlooked as being attributable to SM. Mast cells play important roles in several cardiovascular symptoms. Adventitial mast cells [70] and coronary artery histamine concentrations [71] are increased in patients with coronary spasm compared with patients without cardiac disease. Histamine has well-known effects on cardiovascular function and is arrhythmogenic in many species [72]. Histamine-induced coronary artery spasm may be severe enough to result in

Table 1
Profiles of systemic mastocytosis and clinically comparable gastrointestinal disorders

Disorder	Prostaglandin D ₂	Urinary <i>N</i> - methylhistamine or urinary methylimidazole acetic acid	Urinary 5-HIAA	Serum chromogranin A	Serum tryptase	Serum gastrin	Serum VIP	Flushing	Diarrhea
Systemic mastocytosis	Increased	Increased	Normal	Normal	Increased	Normal	Normal	Yes	+
Gastric carcinoid tumor	No data	Increased	Normal or increased	Increased	No data	Normal or increased ^a	Normal	Yes	+
Zollinger-Ellison syndrome	No data	Increased (active disease)	No data	Increased (active disease)	No data	Increased	No data	No	+
Verner- Morrison syndrome	No data	No data	No data	No data	No data	No data	Increased	Yes	++
Carcinoid syndrome	Normal	No data	Increased	Increased	No data	No data	Normal	Yes	+

Abbreviations: HIAA, hydroxyindoleacetic acid; VIP, vasoactive intestinal polypeptide; +, present; ++, marked.

^a When associated with hypergastrinemic conditions.

downstream myocardial ischemia [73]. Because this effect cannot be blocked by histamine-2 (H_2) receptor antagonists [73], an effect on coronary artery H_1 receptors has been implied. Coronary artery spasm may occur during anaphylaxis, however, despite the previous administration of H_1 -receptor antagonists [74,75], suggesting involvement of other mediators in addition to histamine.

Intravenous infusion of histamine in patients pretreated with the H_2 -receptor antagonist cimetidine resulted in decreased coronary vascular resistance in patients with atypical angina and normal coronary arteries, whereas in two of five patients with spontaneous angina and significant coronary artery disease, histamine infusion caused angina accompanied by ST-T elevation and increased coronary vascular resistance [76]. These findings suggest that the histamine release that occurs in SM may have a detrimental effect on coronary circulation in patients with coronary artery disease or in patients taking H_2 -receptor antagonists. Further support for this hypothesis has come from studies of isolated perfused human hearts removed in the process of cardiac transplantation [77] and in studies of the hearts of non-human species [78]. Exogenous agents, such as the anaphylatoxin C5a, can act on cardiac mast cells, causing release of many mediators in addition to histamine. In one system, the decrease in coronary blood flow and the myocardial dysfunction resulting from intracoronary infusion of C5a were attenuated by the mast cell stabilizer lodoxamide. Although histamine was released, H_1 - and H_2 -receptor blockade had no effect on coronary blood flow or regional cardiac function, suggesting that other released mediators, such as vasoactive eicosanoids, were responsible for these effects [79]. In the dog, administration of intravenous prostaglandin D_2 , a product of mast cells, results in systemic vasodilation, bronchoconstriction, and pulmonary artery vasoconstriction [80]. The benefit of adding aspirin, a cyclooxygenase inhibitor, to the medication programs of patients with SM who are experiencing shock syndrome despite antihistamine treatment suggests that prostaglandin D_2 may contribute to their cardiovascular symptoms [81].

Chest pain, hypotension, and tachycardia can occur during anaphylactic episodes in SM [11], and coronary artery spasm can occur during drug-induced immediate hypersensitivity reactions and during anaphylactoid reactions [74,75]. Mast cell infiltration into coronary artery adventitia also may be important in the evolution of coronary atheromata [82–84], and the proportion of degranulated cardiac mast cells is highest in segments with plaque rupture [85]. These findings suggest another mechanism whereby mast cell degranulation can precipitate or contribute to cardiovascular symptoms in SM.

In a large autopsy series of 100 normal and 92 diseased hearts, the highest mean value for the number of mast cells per high-powered field was in subjects with mast cell neoplasia [86]. Human heart mast cells can be triggered to release histamine by antigen, anti-IgE, anti-Fc ϵ receptor 1 (Fc ϵ RI) [87], the anaphylatoxin C5a [88], general anesthetics [87], and other

nonimmunologic stimuli. Histamine infusion into normal volunteers during cardiac catheterization results in significant decreases in systolic, diastolic, and mean aortic pressures; systemic vascular resistance; left ventricular end-diastolic pressure; and stroke index and in significant increases in heart rate and cardiac output [89]. Cardiac mast cells may therefore be targets and effectors in anaphylactic reactions.

The release of exogenous mediators in addition to mast cell-derived histamine and prostaglandin D₂ has been implicated in cardiovascular responses in SM. Calcitonin gene-related peptide, a 37-amino acid polypeptide synthesized and stored in sensory neurons, has potent vasodilatory activity in several species, including human beings [90–92]. Release of this peptide has been documented in anaphylaxis [93] and during aspirin desensitization in SM [94]. Moreover, the release of calcitonin gene-related peptide can be attenuated by H₁- and H₂-receptor antagonists and the cyclooxygenase inhibitor indomethacin [95].

The cardiovascular symptoms in SM therefore frequently accompany other signs of mast cell mediator release, such as those that occur during generalized mast cell degranulation. Release of histamine and prostaglandin D₂ can have profound hemodynamic consequences. In addition, in the heart itself, cardiac mast cells are in a unique location to cause profound cardiovascular sequelae. These cells, numerically increased in the hearts of patients with SM, can be triggered to degranulate by numerous immunologic and nonimmunologic stimuli.

Neurologic symptoms

Neurologic complaints in SM include headache, dizziness, seizures, and neuropsychiatric complaints. Case reports of individual patients with SM have additionally documented severe and unusual central nervous system manifestations, such as recurrent episodes of loss of consciousness with neuroradiologic signs of chronic brain ischemia [96], chorea [97], mixed pyramidal and neuromyopathic neurologic signs [98], conus medullaris syndrome [99], and progressive neurologic degradation with progressive blindness and lower limb paresis [100]. Nerve–mast cell interactions, such as the ability of various neuropeptides to cause dermal mast cell histamine release, are well known [20,101]. Moreover, mast cells participate directly in several neurologic disorders, including cluster headache [102], and are present in increased numbers in the lesions of multiple sclerosis [103], where they may participate in plaque formation [104].

Headache, which can be generalized or unilateral, is a frequent complaint in patients with SM. In the case of cluster headaches, the close association of mast cells to cutaneous nerve axons has led to the hypothesis that mast cell secretion is triggered by antidromic reflex activity [102,105], and this hypothesis has been supported by ultrastructural studies by other authors [106]. Similarly, the ability of mast cells to secrete proinflammatory

molecules, such as kinins, prostaglandins, and cytokines, and especially vasodilatory molecules, such as histamine, nitric oxide [107], vasoactive intestinal peptide [108], and vascular endothelial growth factor [109], suggests multiple pathways for promotion of migrainous headache pain [110].

In our experience, dysfunction of the autonomic nervous system may be mistaken for symptoms of mastocytosis, as illustrated by the following clinical vignette. A 50-year-old nonatopic man was referred for evaluation of possible mastocytosis. His primary symptom was sweating, which was associated with blood pressure spikes, shortness of breath, palpitations, dizziness, and flushing. Routine medications included oral disodium cromoglycate, fexofenadine, and ranitidine. Attacks were treated with subcutaneous epinephrine, fexofenadine, or diphenhydramine. Levels of mast cell mediators in blood and urine were normal, and the result of a bone marrow biopsy was normal. Subsequently, the result of a thermoregulatory sweat test was abnormal and consistent with essential hyperhidrosis.

In contrast to this patient, in patients who have partial anhidrosis with sweating limited to the face and neck, “flushing,” and heat intolerance, the diagnosis of SM also may be considered. Therefore, a useful question in the evaluation of patients referred for SM is “Do you sweat normally?” If the answer is no, performance of a thermoregulatory sweat test should be considered.

Psychiatric complaints in patients with SM are widely divergent. Some symptoms, such as depression, can be explained by the emotional distress, disability, and helplessness caused by other symptoms of SM, whereas other psychiatric symptoms, such as episodes of rage, impaired attention and memory, amnesia, crying spells, anger, and fatigue, may escape easy explanation [111]. Histamine, for example, does not cross the blood-brain barrier [112], and parenteral injections of histamine do not cause effects on the central nervous system, save for emesis [112] because of its effect on the chemoreceptor trigger zone and vascular headache [113]. Mast cell infiltration in the meninges has been reported only rarely [114].

Although only 1% of orally administered disodium cromoglycate is absorbed from the gastrointestinal tract [115], one study found clinical benefit to disorders of cognitive function in patients administered disodium cromoglycate at a dose of 100 mg four times per day when compared with placebo [116].

Gastrointestinal symptoms

Hepatobiliary symptoms

Hepatobiliary involvement in SM is common but may cause few symptoms. Hepatomegaly was found in 72% of the patients in the series reported by Horny and coworkers [117] and in 41% of those in the series reported by Travis and colleagues [11]; in the latter study, 29% of patients had abnormal results of liver function tests. Mast cells can infiltrate the liver diffusely without

distortion of hepatic architecture, or their infiltration may be associated with mild to moderate portal fibrosis (14% of patients) or, less commonly, cirrhosis (4% of patients) [117]. Portal hypertension has been reported in association with SM [118,119] and has been ascribed in different reports to pre- and postsinusoidal block attributable to mast cell infiltration or to fibrosis [118] and to increased splenic blood flow [120]. The clinical accumulation of ascites may respond to diuretics [121] or may require treatment with interferon- α [122] or surgery (portal diversion) [123]. Interestingly, the antibiotic and mast cell degranulator polymyxin B has been reported to improve many of the clinical findings of SM, including hepatomegaly and ascites [124]. Variceal bleeding seems to be a rare complication of SM-induced portal hypertension and has been managed with splenorenal shunting [125]. Splenectomy in one patient resulted in portal pressure returning to normal [120].

Mast cells are not found in normal splenic tissue [126]. Splenomegaly attributable to mast cell infiltration frequently accompanies hepatomegaly in SM [127,128]. The broad spectrum of histologic manifestations of mast cell infiltrates into the spleen (and lymph nodes) leads to a wide range of differential diagnoses with which these infiltrates can be confused, including T-cell lymphoma, follicular hyperplasia and lymphoma, Kaposi sarcoma, and Langerhans cell granulomatosis [128]. Marked splenomegaly is more common in patients with aggressive mastocytosis [129]. Splenectomy, which is often performed to relieve hypersplenism associated with anemia and thrombocytopenia, seems to prolong survival in patients with aggressive SM and to improve tolerance of chemotherapy [130].

For patients with SM lacking skin lesions or those with mild skin findings that go unnoticed, hepatosplenomegaly and attendant findings of ascites or esophageal varices bring to mind more common ailments, including (1) disorders affecting parenchymal liver cells or supporting tissue; (2) disorders causing obstruction of hepatic or portal veins, lymphatics, or bile canaliculi; and (3) congestive heart failure. Likewise, the detection of splenomegaly by palpation or on CT frequently calls to mind the possibility of hematologic disorders (anemias, myeloid disorders, and lymphomas), reticuloendothelial disorders, infiltrative disorders, and local diseases (eg, cirrhosis, congestive heart failure). In many of these clinical situations, the correct diagnosis may depend on performance of a tissue (eg, bone marrow, liver) biopsy.

General gastrointestinal symptoms

General gastrointestinal complaints in SM are frequently chronic and debilitating. Leading symptoms include gastrointestinal bleeding, abdominal pain, diarrhea, malabsorption, nausea and vomiting, and peptic ulcer disease [131]. Esophageal complaints are infrequent, consisting mainly of esophagitis and occasional esophageal stricture; however, esophageal varices may accompany portal hypertension in SM, and variceal bleeding may be the presenting symptom of SM [132].

In regard to gastrointestinal bleeding, despite the fact that patients with SM secrete increased amounts of histamine (as reflected in increased excretion of the histamine metabolite 1-methyl-4-imidazoleacetic acid [133] or N^ε-methylhistamine [134]) and stimulation of H₂ receptors on parietal cells by histamine facilitates stimulation of acid secretion by gastrin [135], the basal and stimulated gastric acid secretory rates measured in patients with SM have been highly variable [131]. There has been poor correlation of symptoms with the degree of mucosal mast cell infiltration [131,136]. Episodes of gastrointestinal bleeding occurred in an infant with urticaria pigmentosa who had increased heparin activity [137] and may occur in patients with mast cell leukemia [138] and in infants with diffuse cutaneous mastocytosis or bullous mastocytosis [139,140]. Death attributable to hemorrhage from penetrating duodenal ulcer and gastric varices, although rare, has been reported [141].

Abdominal pain in SM has been divided into dyspeptic pain and nondyspeptic pain. Dyspeptic pain, located epigastrically, is associated with a high incidence of peptic ulcers on upper gastrointestinal endoscopy, is relieved by antacids or H₂-receptor antagonists, and is associated with a significantly higher basal acid output than nondyspeptic pain. Nondyspeptic pain is not relieved by these agents, is crampy in nature, and is located in the lower abdomen [142]. Patients with nondyspeptic pain have a normal basal acid output and normal results of upper gastrointestinal endoscopy. Both types of pain have been described in individual patients with SM [143].

In a prospective study of 16 patients with SM by Cherner and coworkers [142], malabsorption was examined with the 72-hour fecal fat excretion test, D-xylose tolerance test, and Shilling test. Of the 16 patients, only 1 had fecal fat excretion more than 11 g/d, 4 had abnormally low D-xylose absorption, and 1 had an abnormally low result on the Shilling test. In other studies, steatorrhea was detected in a wide range (5%–67%) of patients with SM [116,143,144].

Diarrhea is a leading cause of morbidity in SM. Several contributory factors, including release of mast cell mediators, tissue infiltration by mast cells, or possible structural changes, are likely important in causing diarrhea [142]. Hypersecretion of gastric acid [145] and overproduction of prostaglandin D₂ [146] are important causes of diarrhea in SM. To date, there is little evidence that mast cells cause release of gastrointestinal peptides that could alter gastrointestinal motility [22,142].

Diagnosis

For patients with SM who have urticaria pigmentosa, the cause of gastrointestinal symptoms is seldom long in doubt. Ironically, in patients lacking skin manifestations of mastocytosis, who often have aggressive disease with impaired liver function, ascites, malabsorption with weight loss, and splenomegaly with hypersplenism, the diagnosis of SM can be delayed [25]. Three

other disorders can mimic the gastrointestinal symptoms of diarrhea, abdominal pain, and malabsorption common in SM: carcinoid syndrome, Verner-Morrison (vasoactive intestinal peptide [VIP]oma) syndrome, and Zollinger-Ellison (gastrinoma) syndrome (see [Table 1](#)).

Only patients with carcinoid syndrome have increased urinary excretion of the serotonin metabolite 5-HIAA. Additionally, in contrast to patients with SM, patients with carcinoid syndrome can experience bronchospasm and cardiac disease (right heart involvement by endocardial thickening of cardiac valve leaflets, atria, and ventricles) [147,148]. In patients with gastric carcinoid tumors, histamine seems to be the mediator associated with flushing [149], and, for these patients, urinary 5-HIAA is not a reliable tumor marker [150,151]. In contrast to patients with SM, patients with carcinoid syndrome do not experience excessive prostaglandin release and peptic ulcer disease is uncommon [152]. In addition, in distinction to patients with SM, in whom epinephrine administration inhibits mast cell mediator release and improves flushing [153], epinephrine may aggravate facial flushing in carcinoid syndrome [154], a phenomenon that has been associated with release of bradykinin into the hepatic venous blood [155]. More recently, release of bioactive tachykinins [156], such as substance P and neuropeptide K, was documented in patients with carcinoid syndrome.

In the Verner-Morrison syndrome, ectopic release of VIP from a non- β -cell tumor of pancreatic islets leads to watery diarrhea (3 L or more per day in 70% of patients), hypokalemia, and renal failure [157]. Associated symptoms include hypercalcemia, hypophosphatemia, hyperglycemia, and cutaneous flushing. Peptic ulcer disease is uncommon. These tumors are often large by the time they are discovered and frequently contain other peptide hormones as well. As in patients with carcinoid syndrome, those with Verner-Morrison syndrome respond to the somatostatin analogue octreotide, and surgical cures in patients with Verner-Morrison syndrome are possible if the tumor has not metastasized or involved vital structures [158,159].

The Zollinger-Ellison syndrome [160] is caused by excessive release of gastrin from a gastrinoma, a tumor that arises from a non- β -cell tumor of pancreatic islets or from G cells of the duodenum [161]. The excessive release of gastrin results in gastric hypersecretion of acid with resultant severe duodenal and jejunal ulcers. Diarrhea (but not flushing) is a common associated symptom. Patients respond to surgical resection, when possible; otherwise, treatment with H_2 -receptor antagonists or H^+ , K^+ -ATPase inhibitors is effective [162].

Skin symptoms

SM can occur without cutaneous findings [163], or the skin findings may be subtle. For example, in patients with the telangiectatic variant of urticaria pigmentosa, the Darier sign may be negative and pruritus and blisters are rare [164]. Generally, however, urticaria pigmentosa is an important

diagnostic accompaniment of SM in 56% to 100% of cases [164]. Subcutaneous injection of recombinant human stem cell factor induces dermal mast cell hyperplasia, increased systemic levels of mast cell mediators, and enhanced melanization and melanocyte hyperplasia at injection sites [165], thereby suggesting that the enhanced skin pigmentation at sites of urticaria pigmentosa is attributable to an accompanying melanocyte hyperplasia. A recent consensus classification of cutaneous mastocytosis recognizes the following variants: maculopapular cutaneous mastocytosis, plaque type, nodular cutaneous mastocytosis or mastocytoma, telangiectatic mastocytosis, and diffuse cutaneous mastocytosis [26,166]. During the first 3 years of life, blisters may form on lesions of urticaria pigmentosa or they may be the initial sign of cutaneous mastocytosis [167].

Symptoms from cutaneous mastocytosis may accompany the more generalized symptoms of SM described previously, or cutaneous symptoms may be the predominant problem. In adults with SM, pruritus may be severe [168], especially in those with extensive cutaneous involvement [169].

For patients with cutaneous symptoms, flushing is among the most common in SM. Differentiation of the flushing in SM from that of carcinoid syndrome should not present difficulty in most cases because of different mediator profiles, provocative factors, appearance and duration of the flushing, and associated physical findings [170].

Diagnosis

Clinical inspection of the typical maculopapular skin lesions of urticaria pigmentosa and elicitation of a positive Darier sign are often sufficient for diagnosis. The rare telangiectatic variant of urticaria pigmentosa may be difficult to recognize; the Darier sign is commonly negative, and pruritus, purpura, and blisters are not present [139]. Anaphylaxis after Hymenoptera stings occasionally has led to the discovery of urticaria pigmentosa [171,172]. The lesions of urticaria pigmentosa have been the presenting signs of massive eosinophilia [173], acute lymphoblastic leukemia [174,175], and acute myelogenous leukemia [176].

On biopsy of involved skin and staining with toluidine blue, diffuse or dense infiltrates of cells with metachromatically staining granules are found in the papillary dermis, especially around blood vessels [177]. This finding represents a 15- to 20-fold increase in the normal number of mast cells [178]. For patients with adult-onset urticaria pigmentosa, skin biopsy cannot differentiate those with SM from those with urticaria pigmentosa involving the skin only [179], but flushing, diarrhea, weight loss, nausea, and vomiting are found only in patients with SM.

For children with bullous changes, especially when bullous changes precede typical lesions of urticaria pigmentosa, other positive findings, such as the Darier sign or the presence of a great increase in mast cells on a biopsy or Tzanck smear [180], allow differentiation of cutaneous mastocytosis from

other bullous disorders of infancy (including bullous erythema multiforme, pemphigus, and scalded skin syndrome) and from xanthomas, juvenile xanthogranulomas, or pigmented nevi [139,181]. Although bullae in SM generally resolve after children are 1 to 2 years of age, the bullae may be associated with dangerous electrolyte and fluid loss or infection [182], and shock has been reported [183]. Fortunately, in children, there is spontaneous resolution of urticaria pigmentosa in approximately 50% of cases [139], whereas in adults, only approximately 10% experience regression of lesions when followed for more than 10 years [184].

Diffuse and erythrodermic cutaneous mastocytosis commonly presents in newborns shortly after birth [182,185]. Involved areas may appear as red-yellow-brown patches, as orange peel in appearance, or as thickening of the skin. Hemorrhagic blisters, dermatographism, and extensive bullae also may be present [139], and the subsequent development of cutaneous mastocytomas after puberty has been reported [186]. Resolution occurs between the ages of 15 months and 5 years [139]. These children, however, are at risk for not only flushing but for diarrhea, gastrointestinal bleeding, hypotension, shock, and death [183,187,188].

Skeletal symptoms

Skeletal symptoms in SM consist primarily of bone pain, osteoporosis, and fractures. It has been known for more than 40 years that heparin administration can cause osteoporosis [189,190] and that increased numbers of bone marrow mast cells are present in various osteoporotic conditions, such as postmenopausal osteoporosis [191], chronic renal failure [192], and hyperparathyroidism [193]. Mast cell numbers in the bone marrow of men with idiopathic osteoporosis are positively correlated with the 24-hour urine excretion of *N*-methylhistamine, which, in turn, is negatively correlated with bone mineral density of the lumbar spine [28].

Skeletal lesions of SM consist of mixed osteosclerotic and osteolytic areas [194] and are reported in approximately 70% of patients with SM [195]. Osteopetrosis-like osteopathy also has been reported [196]. Symptoms of skeletal involvement in SM are common, with bone pain being reported in 20% or more of patients [11,114,197], fractures in 16% [11], and arthralgias in 9%.

Unlike heparin-induced osteopenia, skeletal lesions in SM also show sclerotic foci, where dramatically increased numbers of mast cells and diffuse marrow fibrosis are present [198]. Bone biopsies in patients with SM have shown high bone remodeling and decreased osteoblast activity [198] but no increase in the numbers of osteoclasts [199,200]. Moreover, characteristic locations of mast cell aggregates in the bone marrow of patients with SM (peritrabecular and perivascular) seem ideal to effect bone remodeling [201,202]. Skeletal scintigraphy in SM has been positive in up to 79% of patients in some series [203], although patients with positive bone marrow findings and negative bone scans also are identified. Bone scans have the

advantage of being noninvasive, and the degree of involvement found on bone scans correlates positively with urinary and plasma histamine levels [204]. The initial and progressive appearances on technetium-99m methyl-enediphosphonate scintigraphy have been used as surrogates for identifying patients with aggressive SM [203].

The osteoblastic and osteolytic skeletal lesions of mastocytosis can be confused with metastatic foci [205], Paget disease, hyperparathyroidism, lymphoma, myelofibrosis, osteopetrosis, and fluoride-related osteosclerosis [194]. In contrast to metastatic lesions, pathologic fractures are unusual in SM and the bones are not weakened [194,206]. In patients with SM who have osteoporosis, however, vertebral collapse can occur [207,208]. In Paget disease, trabecular thickening is organized along lines of stress, occurs in the cortex and in the spongiosa, and tends to enlarge the affected part [205]; in addition, alkaline phosphatase and urinary hydroxyproline levels are increased [209]. When present in SM, diffuse medullary sclerosis may resemble the radiographic appearance of agnogenic myeloid metaplasia; however, scattered osteosclerotic and osteoporotic foci do not occur in agnogenic myeloid metaplasia; when present, they serve to distinguish these two disorders [205]. The presence of skin lesions of urticaria pigmentosa should alert the physician to the possibility of SM; yet, in some patients, osteoporosis may predate dermatologic findings by many years [210]. Increased levels of interleukin-6 recently were detected in the serum of patients with SM who had osteoporosis or bone pain [211].

In SM, the response of bone pain to medications also may serve to distinguish it from other causes of bone pain. For example, treatment with ketotifen resulted in resolution of bone pain, flushing, and pruritus in one patient whose increased plasma and urinary histamine levels returned to normal, as did 1,25-dihydroxyvitamin D₃ and osteocalcin levels [212]. Treatment with interferon- α -2b also has beneficial effects on pain episodes, frequency of vertebral fractures, and trabecular bone mineral density [213,214]. Although mithramycin was beneficial for relieving bone pain in one patient with SM who had bone changes of osteopetrosis [215], this effect is not helpful for distinguishing bone pain in SM from that in other disorders, because mithramycin is also beneficial in symptomatic Paget disease [216]. Intermittent single intravenous infusions of pamidronate have resulted in long-lasting pain control and improved lumbar spine bone density in patients with SM [217]. Severe bone pain without associated pathologic fractures also has responded to oral alendronate [218].

Anticipated symptoms that rarely occur

Because of the nature of the mediators produced by mast cells, certain symptoms might be anticipated to occur more frequently than is actually observed. Bleeding, for example, is a rare complaint of adult patients with SM, aside from the episodes of gastrointestinal bleeding [137,141] that

may occur in patients with mast cell leukemia [138] and in infants with diffuse cutaneous mastocytosis or bullous mastocytosis [139,140]. Although venous bleeding and coagulation times are generally normal [114], prolonged prothrombin time, partial thromboplastin time, and thrombin times are reported in infants with bullous and diffuse cutaneous mastocytosis and gastrointestinal bleeding [140,183]. Increased heparin release was precipitated in a child with urticaria pigmentosa after a "tolerable hot bath" [219]. Other potential causes for otherwise unexplained bleeding episodes in SM include thrombocytopenia associated with bone marrow infiltration by mast cells, local gastrointestinal lesions (eg, peptic ulcers), and vasodilation attributable to histamine and other mediator release [140].

Reports of pulmonary symptoms in SM are rare, despite increased production of prostaglandin D₂ [69] and its known bronchoconstrictor effect [220,221]. Wheezing as an isolated symptom in SM is unusual [63] and generally is associated with episodes of anaphylaxis or with underlying asthma [11]. Bronchial hyperresponsiveness in SM has been reported only rarely [222]. Diffuse pulmonary nodules composed of mast cells were found in one patient with aggressive SM [223]. Because bronchospasm is common in carcinoid syndrome [148] but not in SM, this symptom generally can be useful for differentiating these two disorders. In one report, dyspnea in a 54-year-old patient with long-standing urticaria pigmentosa and pulmonary interstitial mast cell infiltration and mast cell granuloma responded to treatment with interferon- α -2a [224].

Summary

Mast cells produce symptoms by local and remote effects of mediator release and by their presence in increased numbers in normal tissue and bone marrow, where they damage and impair normal organ function. Moreover, mast cells are long-lived and heterogeneous in their response to secretagogues and to inhibitors of mediator release. Clinicians sorting out the diagnosis of SM on the basis of presenting signs and symptoms continue to have their diagnostic skills challenged because of the rarity of this disorder, the fact that many symptoms of SM are present in more common disorders, and the multiple guises that SM may assume at the time of presentation.

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