
CME review article

This educational activity is supported by an educational grant from GlaxoSmithKline

Current approaches to the diagnosis and treatment of systemic mastocytosis

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Objective: To review the clinical manifestations of mastocytosis and examine the recommended diagnostic procedures and therapeutic options available for the treatment of this condition.

Data Sources: PubMed searches were performed for articles published regarding presentation and classification of mastocytosis and the diagnostic criteria and treatment options for this condition using the keywords *mastocytosis*, *clinical features*, *World Health Organization diagnostic criteria*, *management*, *pathogenesis*, and *urticaria pigmentosa*. Retrieved articles were surveyed for additional citations.

Study Selection: Articles were reviewed for relevance to the study objectives, and more recent articles were preferentially included. Prospective studies were preferentially included when available.

Results: Mastocytosis is a heterogeneous disorder that results from clonal mast cell proliferation. Symptoms are typically limited to the skin in the pediatric population, requiring only symptomatic treatment with spontaneous resolution by puberty. Disease course in adults ranges from minimally symptomatic in most to highly aggressive but tends to be persistent. Symptoms can be protean and nonspecific. The mainstay of treatment consists of avoidance of triggers of mast cell degranulation and symptom-based therapy.

Conclusions: Mastocytosis should be suspected in patients who present with a constellation of symptoms, including flushing, abdominal pain, diarrhea, unexplained syncope, and classic urticaria pigmentosa lesions. Diagnosis should be established by a bone marrow biopsy in all adults. Staging should be performed to assess disease burden and evidence of end-stage organ damage. Patients should be offered symptom-based treatment and cytoreductive therapy only for aggressive systemic mastocytosis or an associated hematologic malignant neoplasm.

Ann Allergy Asthma Immunol. 2010;104:1–10.

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INTRODUCTION

Mastocytosis is a heterogeneous disorder characterized by the clonal proliferation of mast cells (MCs), leading to their accumulation in 1 or more organs. The cutaneous

form was first described in 1869, when Nettleship and Tay identified the classic skin lesions of urticaria pigmentosa (UP), now recognized as fixed, reddish brown maculopapular skin lesions. In 1949 Ellis described an autopsy case of a patient with UP who had increased numbers of MCs in the liver, spleen, lymph nodes, and bone marrow, suggesting that mastocytosis may be a systemic disease.¹ Recent consensus conferences on the diagnosis and treatment of mastocytosis have attempted to standardize the nomenclature and diagnostic and treatment criteria to assist physicians in their approach to treating patients with mastocytosis.^{2,3}

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Received for publication June 26, 2009; Received in revised form August 5, 2009; Accepted for publication August 10, 2009.

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doi:10.1016/j.anai.2009.11.006

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PATHOGENESIS

The interaction of the protein ligand stem cell factor to its cognate receptor c-KIT (CD117), a membrane tyrosine kinase receptor, with subsequent activation of KIT kinase activity initiates the signaling pathways critically involved in MC differentiation and survival.⁴ Pathologic activation of KIT due to a mutation in codon 816 replacing aspartic acid for valine (KIT D816V) is associated with up to 93% of patients with systemic mastocytosis (SM).^{5,6} The KIT D816V mutation stabilizes KIT in its active conformation with resultant autophosphorylation and constitutive activation.⁷ c-kit mutations are not consistently detected in all patients with mastocytosis, such as those with childhood-onset cutaneous mastocytosis (CM), although some investigators have postulated that this may be due to methodologic limitations or difficulties in isolating genetic material from specific MC subpopulations. In addition, the presence of the D816V KIT mutation does not predict disease activity, severity, or progression. Thus, the existence of KIT D816V may be necessary to establish a clonal MC population, but other genetic abnormalities that influence SM disease activity remain to be determined. Additional mutations have recently been identified in mastocytosis patients that may coexist with the D816V-KIT mutation.⁸

CLINICAL PRESENTATION

Cutaneous Mastocytosis

Up to 90% of children and adults with mastocytosis may have skin involvement, making skin the most frequently involved organ in mastocytosis. CM is classified based on clinical manifestations in UP, solitary mastocytoma, diffuse CM, and telangiectasia macularis eruptiva perstans (TMEP). In pediatric patients, CM typically appears before the first birthday in 80% of affected individuals, is typically not associated with systemic disease, and in most cases will spontaneously resolve by puberty.^{9,10} This is in contrast to adults who present with CM, who more typically will have evidence of systemic involvement and persistent disease.²

UP consists of fixed, reddish brown lesions that are macular or papular but may also consist of plaques and rarely

nodules or blisters. These lesions urticate in response to physical irritation, which is referred to as Darier's sign. UP lesions tend to be larger, better delineated, and more hyperpigmented in children compared with adults, who tend to have numerous small lesions that coalesce to form mottled areas. The trunk and thigh are more commonly involved with sparing of the face, palms, and soles of the feet.

The solitary mastocytoma is a solitary, reddish brown macule, plaque, or nodule with a positive Darier's sign. It is relatively less common, often presents within the first 3 months of life, and typically resolves spontaneously during childhood.

Diffuse CM is a rare form of CM that presents nearly exclusively during infancy with erythroderma involving the entire skin. It is characterized by diffuse infiltration of the MCs in the dermis, and severe involvement may lead to prematurely aged or thickened skin and is also associated with bullous disease. Darier's sign is pronounced. Unlike other forms of CM, it is frequently associated with systemic disease and may have a more symptomatic course. Complications, including hypotension and gastrointestinal hemorrhage, may occur.^{10,11}

TMEP lesions consist of telangiectatic macules over a background of tan-brown colored skin. It typically develops in adults, although there have been reports of TMEP in children,¹² and it may coexist with UP lesions.¹³

Systemic Mastocytosis

The symptoms of SM are secondary to MC mediator release or MC infiltration into affected tissues. SM is uncommonly diagnosed in children but frequently diagnosed in adults. The symptoms of SM are protean and nonspecific, including flushing, dyspeptic abdominal pain, diarrhea, recurrent syncope, bone pain, and fatigue (see Table 1 for complete list).^{14–22} Gastrointestinal symptoms can be exacerbated by spicy foods, alcohol, and stress, are chronic, and can be a cause of considerable morbidity. Bone pain typically involves the long bones and pathologic fractures can occur. Constitutional symptoms, such as weight loss, fevers, and chills, are more common when SM coexists with a hematologic non-MC malignant neoplasm or in aggressive SM (ASM). Given the varied and nonspecific nature of its presentation, the diagnosis of SM may be delayed in the absence of cutaneous symptoms. Thus, a combination of suggestive symptoms along with identification of characteristic UP lesions should raise the suspicion of SM. SM may also present with signs of MC infiltration, leading to organomegaly (hepatomegaly, splenomegaly, and lymphadenopathy) or cytopenias (anemia, thrombocytopenia). In advanced cases there may be manifestations of end-organ damage as a result of MC infiltration, such as portal hypertension with ascites.

Children rarely present with systemic disease; however, when this disease is present, it usually consists of episodic flushing or diarrhea.^{23–26} There have been case reports of children with CM who had anaphylactic episodes, although in

Table 1. Clinical Features of Mastocytosis

Clinical features	Patients, %								
	Demis ¹⁴ (n = 113)	Mutter et al ¹⁵ (n = 29)	Webb et al ²⁰ (n = 26)	Yam et al ²² (n = 13)	Cherner et al ¹⁷ (n = 16)	Travis et al ¹⁸ (n = 58)	Horan et al ¹⁶ (n = 21)	Pagano et al ¹⁹ (n = 24)	Lim et al ²¹ (n = 342)
Gastrointestinal									65
Abdominal pain	23	48	40	46	80	35	81	17	
Diarrhea	23	28	40	54	63	24	67	8	
Nausea and/or vomiting	23	45	28	31	NA	21	57	17	
Gastrointestinal bleeding	23	24	NA	8	NA	7	5	NA	
Peptic ulcer disease	4	14	24	31	44	36	24	17	
Malabsorption	NA	NA	NA	NA	25	5	24	NA	
Hepatomegaly	12	83	45	77	NA	41	38	46	27
Splenomegaly	11	86	50	62	NA	48	19	50	37
Cutaneous									
Urticaria pigmentosa	99	83	56	54	75	53	81	33	41
Pruritus	NA	NA	44	8	88	53	81	11	53
Flushing	36	28	32	15	44	21	95	21	NA
Cardiovascular									
Tachycardia	18	NA	12	NA	31	5	28.6	25	NA
Syncope	NA	NA	20	NA	NA	NA	NA	12	NA
Anaphylaxis	NA	NA	NA	NA	25	14	38	8	17
Central nervous system									
Headache	0	17	20	NA	19	10	90.5	12	
Organic brain syndrome	NA	NA	NA	NA	NA		76	NA	
Musculoskeletal									
Osseous lesions	9	NA	71	NA	75	NA	NA	33	31
Bone pain	NA	28	20	NA	19	19	9.5	29	
Constitutional ^a	12	41	56	46	25	55	Several	25	42
Respiratory									
Lower respiratory tract	6	NA	20	NA	NA	4	9	NA	NA
Rhinitis	NA	10	NA	NA	NA	NA	57	NA	NA
Lymphadenopathy	NA	35	40	NA	19	26	NA	25	21

Abbreviation: NA, not reported.

^a Constitutional indicates weakness, fatigue, and general malaise.

many cases a diagnostic bone marrow biopsy was not performed to rule out SM.²⁷

Pregnancy

Worobec et al²⁸ described 8 women with indolent SM (ISM) who gave birth to 11 healthy children. One third had mild exacerbation of their symptoms during pregnancy. No adverse reaction with anesthesia and no complications during labor and delivery were observed.

COMMON CLINICAL SCENARIOS ENCOUNTERED DURING EVALUATION OF SUSPECTED SM

Chronic Idiopathic Urticaria vs UP

Refractory chronic idiopathic urticaria (CIU) may raise the suspicion of CM or SM because the lesions of UP contain increased numbers of MCs and form a wheal-and-flare response with rubbing or other triggers of MC degranulation. There are, however, distinct differences between hives and UP lesions. Hives typically resolve in less than 24 hours without any residual scarring, whereas UP consists of fixed, reddish brown maculopapular lesions that

urticate with scratching and resolve back to the fixed maculopapular lesion. UP lesions typically spare the palms, soles, and face, whereas hives may be present on any part of the body. Thus, CIU can be differentiated from UP on clinical grounds alone, and a clinical course suggestive of CIU is typically not a manifestation of CM or SM.

Mastocytosis and Hymenoptera Venom

There are several case reports of venom anaphylaxis as the presenting complaint of SM.^{29–32} Bonadonna et al³³ reported on 379 patients with systemic reactions to stinging insects. Four patients had negative skin and CAP test results to Hymenoptera venoms but had elevated tryptase levels (22.7–42 ng/mL). Among these 4 patients, 3 were diagnosed as having ISM and 1 had a clonal MC activation syndrome revealed by a bone marrow biopsy specimen. Therefore, the absence of IgE to Hymenoptera venom by skin or blood testing in a patient with a clinical presentation suggestive of venom anaphylaxis should raise the suspicion of SM. A serum tryptase level should be obtained; if elevated, patients

should undergo a bone marrow examination. In addition, recent studies^{33,34} have suggested that a rare clonal MC subpopulation can sometimes be identified even in patients not meeting criteria for SM, although the significance of this subpopulation is unclear.

Interestingly, in the article by Bonadonna et al 44 patients (11.6%) with a history of venom anaphylaxis had a baseline serum tryptase greater than 11.4 ng/mL. Of the 30 patients who tested positive for venom allergy and consented to have a bone marrow study performed, 18 were found to meet criteria for ISM (including 6 patients who had a tryptase level <20 ng/mL), 8 had evidence for abnormal MCs without meeting full World Health Organization (WHO) criteria for mastocytosis, and 4 were healthy.³³ Thus, patients with abnormal MC subpopulations who may be experiencing progression to diagnosable SM or have minimally symptomatic indolent disease may be predisposed to anaphylactic reactions to venom or other triggers and potentially can be identified with elevated baseline serum tryptase levels after recovery from an anaphylactic event.

Recurrent Anaphylaxis

Akin et al³⁴ reported that of 24 patients seen at a tertiary referral center for evaluation of idiopathic anaphylaxis, up to 50% had characteristic UP lesions and/or SM. In a retrospective review of anaphylaxis in 601 patients, 3 were found to have SM.³⁵ Thus, anaphylaxis may be a presenting symptom of SM, especially in adults. Presence of other MC mediator-related symptoms, such as flushing and diarrhea, should raise suspicion of SM. On the other hand, the presence of event-related urticaria, angioedema, and wheezing tend to favor idiopathic anaphylaxis.³⁵

DIAGNOSIS

Mastocytosis is first suspected on clinical grounds, including identification of UP lesions and recognition of compatible MC mediator-related symptoms. Because SM is a disorder of clonal proliferation of MCs, the diagnosis is established by detection of MCs with abnormal morphologic features and immunophenotypes in the bone marrow or other extracutaneous organs and specific mutations in its growth factor (c-KIT) receptor (Fig 1 and Table 2). Serum or urinary histamine examinations are influenced by dietary ingestion, may vary with handling and processing, and are currently not included as part of the diagnostic criteria for SM.

HISTORY AND PHYSICAL EXAMINATION

The most common and at times sole manifestation of disease may be the pigmented fixed maculopapular skin lesions (UP). Presence of MC mediator release symptoms may also raise suspicion of the disease (Table 1). Physical examination should include inspection for skin lesions, eliciting Darier’s sign (if present), and palpating for hepatosplenomegaly and lymphadenopathy.

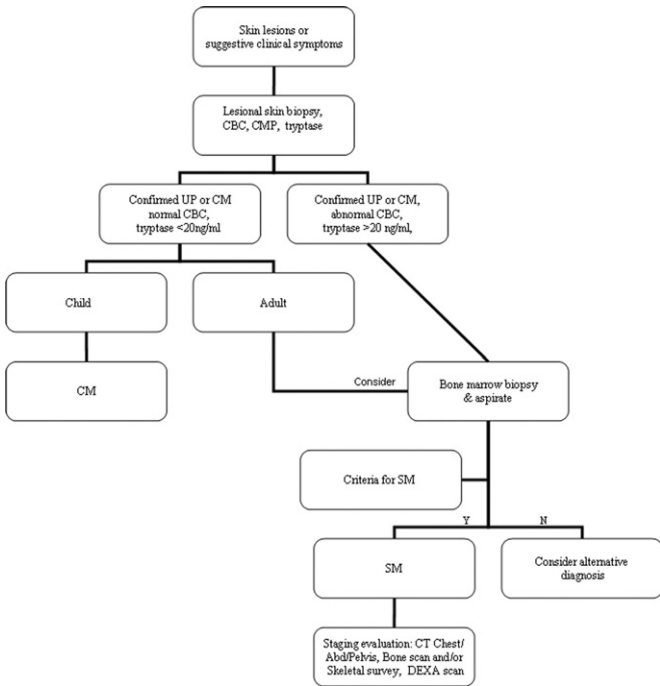


Figure 1. Diagnostic algorithm for suspected mastocytosis.^{2,3} Abd indicates abdomen; CBC, complete blood cell count; CM, cutaneous mastocytosis; CMP, complete metabolic panel; CT, computed tomography; DEXA, dual X-ray absorptiometry; SM, systemic mastocytosis; UP, urticaria pigmentosa.

Table 2. World Health Organization Diagnostic Criteria for Mastocytosis^{2,3}

Cutaneous mastocytosis
Typical clinical signs (UP, DCM, solitary mastocytoma, TMEP)
Presence of at least 1 of the following in a skin lesion:
1. Focal dense infiltrates (>15 MCs per cluster) or diffuse MC infiltrates (>20 cells per high-power field)
2. c-KIT D816V mutation
Systemic mastocytosis
Presence of at least 1 major and 1 minor criterion or 3 minor criteria in the bone marrow or other extracutaneous organ:
Major
Multifocal dense infiltrates of MCs (>15 MCs in aggregates)
Minor
1. MC infiltrates contain >25% spindle-shaped cells or other atypical morphologic features
2. c-KIT D816V mutation
3. Expression of CD2 and/or CD25 on CD117 ⁺ MCs
4. Serum tryptase levels >20 ng/mL (not valid if patient has concomitant hematologic disorder)

Abbreviations: DCM, diffuse cutaneous mastocytosis; MC, mast cell; UP, urticaria pigmentosa; TMEP, telangiectasia macularis eruptiva perstans.

SKIN BIOPSY

A skin biopsy with staining specific for MC (toluidine blue, Wright-Giemsa) and tryptase immunohistochemical analysis

should be strongly considered in all patients with characteristic skin lesions. Tryptase immunohistochemical analysis is a reasonably specific marker for the detection of MC. A blind skin biopsy is not recommended in the absence of UP lesions. CM is diagnosed on the basis of skin examination and specific histologic and molecular criteria (Table 2).²

SERUM TRYPTASE MEASUREMENT

Tryptase is a MC protease that is used as a surrogate for MC activation or body MC load, and a value exceeding 20 ng/mL is the cutoff defined per WHO diagnostic criteria for the diagnosis of SM (Table 2). The test has a specificity of 98% and a sensitivity of approximately 83% to 93% for diagnosing SM at tryptase levels greater 20 ng/mL.^{36,37} Patients with compatible clinical symptoms and tryptase levels of less than 20 ng/mL can still have detectable abnormalities in the MC lineage; for example, in a recent study of 15 patients presenting with venom anaphylaxis who had positive allergy test results to venoms and a baseline serum tryptase level greater than 11.4 ng/mL but less than 20 ng/mL, 6 patients met the criteria for ISM.³³ Serum tryptase levels are typically normal to slightly elevated in patients with CM, may be transiently elevated during acute anaphylaxis, and are slightly increased in end-stage renal disease. These levels may also be elevated in myeloid neoplasms, acute myeloid leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, refractory anemia, and hypereosinophilic syndrome.³⁸ Thus, elevated tryptase levels are only indicative of SM in the absence of other hematologic malignant neoplasms.

BONE MARROW EXAMINATION

A bone marrow examination (biopsy and aspirate with specimens for flow cytometry) constitutes the most important step in diagnosing SM. It is not typically required in most pediatric patients with CM unless the patient has cytopenias, other hematologic abnormalities, or other symptoms that suggest target organ involvement with MCs. Histologic and molecular criteria have been established in WHO reference documents that define SM based on consensus proposals published in 2001³ (Table 2).

Bone Marrow Histologic Analysis

Tryptase immunohistochemical analysis is the marker of choice to detect MCs. MCs may be difficult to identify in routine hematoxylin-eosin-stained sections and can be missed unless special metachromatic stains, such as Wright-Giemsa or toluidine blue, are applied. Multiple focal accumulations of MCs in the bone marrow (>15 MCs per aggregate) are pathognomonic for mastocytosis and are the major criteria used in the diagnosis. These infiltrates are most commonly located paratrabecularly, but perivascular and parafollicular distributions are found. Typically, more than 25% of the MCs in these lesions are spindle shaped (abnormal morphologic features) in the aspirate smear or biopsy section, a minor criteria used in the diagnosis of mastocytosis. Less commonly, most MCs in the lesions are round, in which

case additional immunohistochemical markers can be used to confirm the diagnosis.³

Aberrant Immunophenotype and Flow Cytometry

Normal MCs express CD117 but not CD2 or CD25; abnormal MCs found in SM have aberrant expression of CD25 and/or CD2.³⁹ Therefore, flow cytometry studies of bone marrow preparations demonstrating coexpression of CD2 and/or CD25 in CD117⁺ (KIT) MCs are evidence of abnormal MCs. This phenotype can often also be identified by immunohistochemical analysis.^{39,40}

KIT-D816V and Other KIT Mutations

Unfractionated bone marrow cells or marrow mononuclear cells should be studied for KIT mutations because these are observed in up to 93% of patients. Several techniques for detection of KIT D816V have been reported in the literature, the most sensitive of which use polymerase chain reaction-based approaches.² If the test result is negative, then DNA sequencing may be performed to screen for other KIT mutations.

HISTOLOGIC DIAGNOSIS OF SM IN EXTRAMEDULLARY TISSUES

Extramedullary tissues (excluding skin) may be examined for the presence of MCs to make the diagnosis of SM, but this approach is not recommended if a bone marrow examination can be performed. The spleen and sinusoids of the liver do not normally contain MCs; therefore, detection of any MCs suggests the diagnosis of SM.⁴¹ Because the number of MCs in lymph nodes and the intestinal tract varies, the detection of dense focal infiltrates of MCs with abnormal morphologic features is required to establish the diagnosis of SM in these organs. Absence of MCs does not necessarily exclude the presence of organopathy due to SM because MCs may be difficult to identify and target organ effects may be due to mediator release and not exclusively tissue infiltration.

STAGING EVALUATION

Once the diagnosis of SM is made, a number of staging investigations are required to define the subtype of disease. Aggressive disease is characterized by progressive infiltration of various organs by MCs, with resultant end organ dysfunction; these findings are termed *C findings*³ (Table 3). MC infiltration with organomegaly but without end organ dysfunction is termed a *B finding* and may occur in a subvariant of ISM (smoldering systemic mastocytosis) with high MC burden (Table 3). Staging investigations may include computed tomography of the chest, abdomen, and pelvis, bone scan or skeletal survey, and a bone density scan (Fig 1). Other testing can be performed based on clinical symptoms.

WHO CLASSIFICATION

Patients with mastocytosis are classified into subgroups based on the WHO consensus criteria.³ Cases fall into 1 of 2 categories: CM or SM. CM is typically limited to the skin

Table 3. B- and C-Findings in Systemic Mastocytosis

B findings	C findings
Hepatomegaly	Hepatomegaly with ascites or portal hypertension
Splenomegaly	Splenomegaly with hypersplenism
Lymphadenopathy	Gastrointestinal tract: malabsorption with hypoalbuminemia and weight loss
Bone marrow: hypercellular marrow; mild dysplasia; myeloproliferation; MC infiltration in bone marrow, >30%; tryptase, >200 ng/mL	Skeleton: lytic bone lesions, osteoporosis with pathologic fractures
	Cytopenias: ANC, <1,000/ μ L; hemoglobin, <10 g/dL; platelets, <100,000/ μ L

Abbreviations: ANC, absolute neutrophil count; MC, mast cell.

without any systemic involvement. SM is further divided into ISM, ASM, SM with associated clonal hematologic non-MC lineage disease (SM-AHNMD), MC leukemia (MCL), and MC sarcoma. These subgroups are based on the severity of disease; for example, ISM is characterized by benign disease with the absence of both C findings and AHNMD. On the other hand, ASM is a rapidly progressive aggressive disease with the presence of C findings. MCL and MC sarcoma are rare variants; patients with these variants have a poor prognosis. Outside MCL and MC sarcoma, other variants of mastocytosis are not considered malignant neoplasms. This classification allows estimation of the patients' prognosis and helps determine the need for cytoreductive therapy (Fig 2 and Table 4).

TREATMENT

Given its highly variable presentation, SM therapy should be tailored according to an individual's disease symptoms. Management includes counseling patients about the disease, avoidance of triggers that can cause MC degranulation, and providing relief of MC mediator-related symptoms. Cytoreductive therapy is only indicated in patients with target organ damage due to SM, typically patients with ASM, SM-AHNMD, and MCL disease categories. Hence, patients who

experience MC mediator-related symptoms, such as chronic gastrointestinal symptoms or even recurrent anaphylaxis, but who do not have C findings per WHO guidelines would not be considered to have ASM and thus typically would not be candidates for cytoreductive therapy.

AVOIDANCE MEASURES

Patients, their caretakers, and their primary care physicians should be informed of the elevated risk of anaphylactoid reactions among this patient population. Treatment of such reactions consists of administration of intramuscular epinephrine (0.3 mg, 1:1,000) and H₁ and H₂ antihistamines. Thus, all patients should be adequately trained in the correct use of a self-injectable epinephrine pen. They should be advised to have it readily available at all times and to seek immediate medical attention in the event of administration.

Avoidance of triggering factors is a major component of SM management. Patients should be cautioned about avoidance of drugs and other triggers, such as alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, intense exercise, and stinging insects, especially if they have do not have a history of safely tolerating them. Individual patients may have variable tolerance patterns, and avoidance lists (Table 5) should be individualized as much as possible. Some muscle relaxants and inducing agents used in general anesthesia may induce MC mediator release.^{42–44} Propofol, vecuronium, tramadol, and fentanyl are considered safe. Radiocontrast medium may provoke anaphylactoid reactions; hence, all patients should be premedicated with steroids and antihistamines before receiving iso-osmolar radiocontrast media. Gadolinium typically does not provoke MC degranulation. MC degranulation is known to occur after NSAID administration in sensitive patients. Given the heterogeneity of NSAID-induced reactions among this patient population, the decision to treat with NSAIDs is individualized. Ketorolac, however, is a potent NSAID and is generally contraindicated in patients with SM.

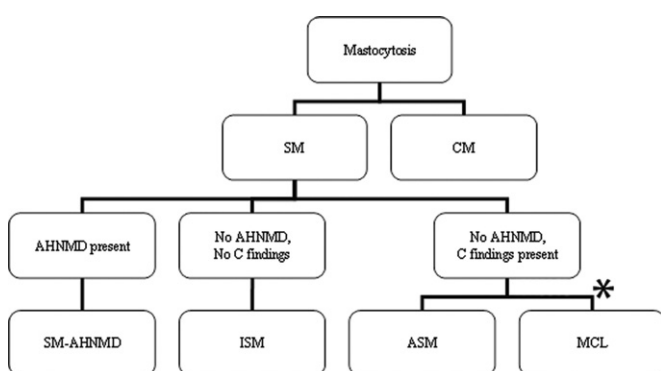


Figure 2. World Health Organization classification of mastocytosis.^{2,3} AHNMD indicates associated clonal hematologic non-mast cell lineage disease; ASM, aggressive systemic mastocytosis; BM, bone marrow; CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; SM, systemic mastocytosis. *More than 10% immature MCs in peripheral blood or more than 20% immature MCs in BM smear.

MANAGEMENT OF MC MEDIATOR-RELATED SYMPTOMS

Symptom control is central to the management of all categories of mastocytosis. For patients with CM only, options include antihistamines for pruritus and in selected cases psoralen–UV-A, topical steroids with occlusive

Table 4. World Health Organization Categories of Mastocytosis

Category	Features
CM	Most common category in children, without any systemic involvement, typically regresses by adolescence. Serum tryptase typically <20 ng/ μ L. Bone marrow biopsy not required in absence of clinical symptoms in pediatric patients.
ISM	Most common subtype in adults. Relatively long duration between symptom onset and diagnosis. Good prognosis in most patients with normal life expectancy. Patients have a high prevalence of UP-like skin lesions, cutaneous symptoms, and mediator-related symptoms and can also have anaphylactoid reactions and GI symptoms. Serum tryptase typically >20 ng/ μ L. Bone marrow biopsy is indicated to rule out AHNMD or high marrow MC load. Leukemic transformation is rare. Patients with B findings may be categorized as having smoldering SM, a subvariant of ISM.
SM-AHNMD	SM may be associated with MPD or MPS or myeloid leukemia in up to 40% of patients. Prognosis depends on the associated hematologic disorder with a median survival of 24 months. Greater frequency of constitutional symptoms, hepatosplenomegaly, and lymphadenopathy. Patients may have significant leukocytosis, anemia, thrombocytopenia, and eosinophilia.
ASM	SM associated with C findings. Rare category (12%). Poor prognosis; median survival, 41 months. May not have associated skin findings. Tryptase levels markedly elevated. Constitutional symptoms, hepatosplenomegaly, lymphadenopathy, anemia, thrombocytopenia, leukocytosis, and eosinophilia more common.
MCL	Exceedingly rare (<1%). MCs are found in peripheral blood. Tryptase level very high. Poor prognosis; median survival, 2 months. ²¹
MC sarcoma	Malignant, invasive solid MC tumor. Exceedingly rare. Poor prognosis.

Abbreviations: ASM, aggressive SM; CM, cutaneous mastocytosis; ISM, indolent SM; MC, mast cell; MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHNMD, SM with associated clonal hematologic non-mast cell lineage disease.

Table 5. Factors That Trigger Mast Cell Degranulation in Patients With Mastocytosis

Category	Examples
Physical stimuli	Heat, cold, friction, pressure, excessive sunlight, intense exercise
Emotional factors	Stress, anxiety
Drugs	Aspirin, NSAIDs, thiamine, alcohol, morphine, codeine, polymyxin-B, amphotericin B, quinine, dextromethorphan, anticholinergic preparations, vancomycin, α -adrenergic blockers
General anesthesia	Succinylcholine, D-tubocurarine, metocurine, doxacurium, atracurium, mivacurium, rocuronium, etomidate, thiopental, enflurane and isoflurane, lidocaine
Venoms	Snakes, stinging insects
Polymers	Dextran
Miscellaneous	Radiocontrast media

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

dressings, or targeted laser therapy for the management of widespread or discrete lesions. Surgical excision of solitary lesions can be curative. Recommended therapeutic options for symptoms related to mediator release in patients with ISM are summarized in Table 6. Because histamine is a central MC mediator, treatment with antihistamines is appropriate in these patients. Newer-generation antihistamines are preferred over older-generation agents such as doxepin for control. Oral cromolyn sodium (Gastrocrom) has limited intestinal absorption and is mostly used to help control gastrointestinal symptoms. The recommended adult dosage is 200 mg 4 times a day, and in children, doses ranging from 60 to 100 mg 4 times per day have been used. Gastric hypersecretion is treated with H₂ antihistamines and proton pump inhibitors; osteoporosis with calcium, vitamin D, and bisphosphonates; and anaphylactoid reactions with epinephrine.

CYTOREDUCTIVE TREATMENT

Cytoreductive therapy is typically reserved for patients with ASM, SM-AHNMD, and MC malignant neoplasms, where the benefits of therapy outweigh the risks of the treatment. Imatinib mesylate is a tyrosine kinase inhibitor that inhibits a number of receptor tyrosine kinases, including c-kit, c-abl, bcr-Abl, and platelet-derived growth factor receptor (PDGFR).⁴⁵ It has recently been approved by the Food and Drug Administration for use in patients with ASM without D816V c-Kit mutation (or c-Kit mutation status unknown).⁴⁵ Because in vitro studies have demonstrated that cell lines carrying the D816V c-kit mutation are resistant to imatinib, imatinib is useful only in patients who do not have the KIT D816V mutation.⁴⁵ Thus, in patients with SM and wild-type c-kit (unfortunately <10% of cases), it may decrease bone marrow MC burden, serum tryptase levels, and control clinical symptoms.⁴⁶ Presence of the *FIP1L1/PDGFR α* fusion

Table 6. Management of Mast Cell Mediator-Related Symptoms

Symptom	Initial therapy	Subsequent therapy	Additional therapy
Pruritus	H ₁ antihistamines	Add H ₂ antihistamines	Add LTRA
Flushing	H ₁ antihistamines		
Recurrent anaphylaxis	H ₁ and H ₂ antihistamines, self-injectable epinephrine	Consider oral glucocorticoids	
PUD	PPI	H ₂ antihistamines	
Diarrhea, nausea, vomiting, abdominal pain	H ₂ antihistamines	Add cromolyn	Consider LTRA, oral glucocorticoids
Malabsorption	Cromolyn	Consider oral glucocorticoids	
Osteoporosis	Calcium and vitamin D	Add bisphosphonate as primary therapy	Consider interferon alfa ^a
Bone pain	Non-NSAID analgesia	Controlled trial of NSAIDs under observation	Radiation therapy for severe localized bone pain; pain consultation
Neurologic symptoms	H ₁ and H ₂ antihistamines	Add cromolyn	

Abbreviations: LTRA, leukotriene antagonist; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

^a For severe osteoporosis.

gene, associated with the myeloproliferative variant hyper-eosinophilic syndrome or chronic eosinophilic leukemia, also confers imatinib sensitivity. Thus, a trial of imatinib should be considered in patients with ASM who lack the D816V mutation or who have eosinophilia with a positive *FIP1L1/PDGFRα* fusion gene.⁴⁵ These patients are said to have an overlap syndrome of SM-chronic eosinophilic leukemia and typically have absolute eosinophil counts greater than 1,500/ μ L with elevated serum tryptase levels.

Other agents used for cytoreductive treatment in patients with aggressive disease and C findings include interferon alfa 2b with or without glucocorticoids and cladribine. Because these medications may be mutagenic and have other adverse effects, their use is only recommended in aggressive disease. Indications for their use include rapidly progressive ASM and MCL. A total of 15% to 20% of patients with ASM treated with interferon alfa 2b demonstrate a clinical response.⁴⁷ Cladribine decreases MC burden, although not all patients with ASM respond.⁴⁸ Patients with SM-AHNMD should be treated for each clinical disorder as if the other was not present. Massive splenomegaly associated with hypersplenism or portal hypertension may be an indication for splenectomy.^{45,49} Because SM is not a malignant neoplasm in most cases, traditional chemotherapy regimens have limited efficacy and results of bone marrow transplantation have been mixed with cases of persistent posttransplantation SM reported.⁵⁰

FOLLOW-UP

The frequency of follow-up depends on the type of SM, presence of mediator-related symptoms, coexisting disorders, and therapy. ISM should have at least a yearly follow-up; serum tryptase levels should be monitored, especially if MC mediator-related symptoms are present, and complete blood cell count and complete metabolic panel should be checked

yearly. Patients with smouldering systemic mastocytosis (a category of ISM with high disease burden) need more frequent follow-up. Progression to MCL or SM-AHNMD is rare; however, if suspected, it should be evaluated by an additional bone marrow examination.

PROGNOSIS

ISM is characterized by minimal symptoms, stable clinical course, and a nearly normal life span. It is uncommon for ISM to progress to severe disease.³ On the other hand, patients with SM-AHNMD, ASM, or MCL tend to have poorer prognosis, with a reduced 5-year survival for patients with SM-AHNMD and a survival duration of approximately 6 months in patients with MCL.^{4,39}

CONCLUSIONS

Mastocytosis is a heterogeneous disease that has diverse clinical implications based on the age of the patient (pediatric vs adult) and the presence and degree of organ involvement (cutaneous vs systemic and then with organ involvement and B findings vs target organ damage with C findings). The diagnostic criteria have been established by consensus panels and validated by numerous clinical studies; the diagnosis of SM made by surrogate blood or other markers in the absence of a tissue diagnosis is not within the standard of care of SM patients.¹⁻⁴ Careful diagnostic and staging procedures should be performed to offer appropriate symptom-based treatment and cytoreductive therapy when indicated. Although the molecular pathogenesis involving c-kit D816V mutations in affected MC is now established, future studies may articulate additional genetic abnormalities that influence disease progression and survival and speed the development of targeted, rationally designed therapeutics for patients with both CM and SM.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

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CME Examination

1–5, Bains SN. 2010;104:1–10.

CME Test Questions

1. Imatinib is indicated in the treatment of all the following EXCEPT:
 - a. indolent systemic mastocytosis
 - b. aggressive systemic mastocytosis
 - c. gastrointestinal stromal tumor
 - d. chronic eosinophilic leukemia
 - e. chronic myeloid leukemia
2. What is the most common cutaneous manifestation of mastocytosis?
 - a. urticaria pigmentosa
 - b. hives
 - c. atopic dermatitis
 - d. solitary mastocytoma
 - e. telangiectasia macularis eruptiva perstans
3. Which of the following medications is least likely to cause mast cell activation?
 - a. morphine
 - b. succinylcholine
 - c. vancomycin
 - d. tramadol
 - e. ketorolac
4. What is the most common point mutation of c-kit in patients with mastocytosis?
 - a. ASP 618 VAL
 - b. ASP 816 VAL
 - c. VAL 816 ASP
 - d. VAL 618 ASP
 - e. VAL 560 GLY
5. Diagnostic criteria for systemic mastocytosis include all of the following EXCEPT:
 - a. aggregates of more than 15 mast cells per cluster in a bone marrow biopsy specimen
 - b. more than 25% spindle-shaped cells in lesional mast cells in a bone marrow biopsy specimen
 - c. more than 2 episodes of unexplained anaphylaxis
 - d. expression of CD2 and/or CD25 on CD117⁺ mast cells in a bone marrow biopsy specimen
 - e. serum tryptase level greater than 20 ng/mL in the absence of concomitant hematologic neoplasm

Answers found on page 41.