INTRODUCTION — Mastocytosis describes a group of disorders in which pathologic mast cells accumulate in tissues. These diseases can be limited to the skin (cutaneous mastocytosis [CM]) or involve extracutaneous tissues (systemic mastocytosis [SM]).

The evaluation and diagnosis of the different forms of CM and SM will be reviewed here. Other issues related to mastocytosis and the biology of mast cells are discussed separately. (See "Mastocytosis (cutaneous and systemic): Epidemiology, pathogenesis, and clinical manifestations," and "Treatment and prognosis of systemic mastocytosis," and "Mast cells: Development, identification, and physiologic roles," and "Mast cells: Surface receptors and signal transduction").

INITIAL APPROACH TO THE PATIENT — An evaluation for a mast cell disorder is appropriate in a patient with manifestations of mast cell activation, such as flushing, tachycardia, diarrhea, fatigue or musculoskeletal pain, or hypotensive syncope or near syncope affecting at least two organ systems. Patients may present with recurrent episodes of anaphylaxis or less severe symptoms suggestive of allergic reactions, for which no consistent trigger or cause has been identified.

History and physical examination — Symptoms can be present in a daily basis or can be episodic. Each episode of symptoms that the patient can describe should be reviewed to determine if the signs and symptoms are consistent with mast cell activation. The physical exam must include a meticulous skin inspection to look for lesions of urticaria pigmentosa (UP) (picture 1) or mastocytomas (picture 2). Descriptions and additional images of characteristic skin lesions are presented elsewhere. (See "Mastocytosis (cutaneous and systemic): Epidemiology, pathogenesis, and clinical manifestations").

If lesions of UP are detected, then the examiner may lightly rub, scratch, or stroke a small area of the affected skin. The development of erythema or urticaria over/around the lesion is called Darier's sign and is pathognomonic for the presence of mast cells within the lesion. However, lesions consistent with mastocytomas (localized accumulations of mast cells) (picture 2) should not be rubbed or scratched, as this may lead to generalized flushing and hives. Instead, the patient or caretaker can usually report that these symptoms occur if the lesion is disturbed.

Skin biopsy — Patients with lesions consistent with cutaneous mastocytosis (CM) should undergo a punch biopsy of skin lesions with specific histopathologic stains, if there is any doubt about the diagnosis. Skin biopsy findings in the context of the morphologic lesion are diagnostic of CM, although skin biopsy does not provide information about systemic involvement. Patients who are not already taking an H1 antihistamine regularly should take a dose prior to biopsy to reduce the effects of mediator release during the procedure.

Specimens should be fixed in formalin and undergo histopathologic staining with Giemsa and/or immunohistochemical staining for tryptase and c-kit. Techniques for identifying mast cells in tissues are presented in detail separately. (See
Laboratories — The following laboratory tests are recommended for a patient suspected of having mastocytosis:

- Complete blood count with differential
- Liver function tests (including serum aminotransferases and alkaline phosphatase)
- Serum tryptase

In addition, the measurement of metabolites of mast cell activation (including 24-hour urine for N-methyl histamine and 11-beta-prostaglandin F2) may be performed, to provide further evidence of mast cell activation.

When to refer — When possible, the following patients should be referred to an allergy/immunology or hematology expert with knowledge of mast cell disorders:

- Any patient suspected of having UP
- Patients with signs or symptoms suggestive of systemic mastocytosis (SM)
- Patients with elevated tryptase levels
- Patients with recurrent unexplained anaphylaxis with hypotension

In addition, among patients in whom the diagnosis of SM has already been made:

- Those with mastocytosis and hematologic abnormalities should be referred to a hematologist for management of the hematologic disorder
- Those with aggressive mastocytosis should be referred to a hematologist for consideration of cytoreductive therapy

Indications for bone marrow examination — It can be difficult to distinguish CM from SM solely on clinical grounds, since patients with CM often have systemic symptoms caused by mast cell mediators and their actions on various tissues and organs.

Adults — It is recommended that all adult patients with UP undergo bone marrow biopsy and aspiration, even if other signs and symptoms of systemic disease are not apparent, as the incidence of systemic disease in this population is high. In addition, patients with the symptoms or laboratory features below may be considered for workup for SM regardless of the presence of skin lesions, particularly if there is an elevated baseline tryptase level.

These symptoms and laboratory features include:

- Unexplained flushing or anaphylaxis, particularly associated with documented hypotensive episodes
- Unexplained gastrointestinal abnormalities (eg, peptic ulcer disease, malabsorption, or diarrhea)
- Unexplained peripheral blood abnormalities
- Unexplained hepatomegaly, splenomegaly, or lymphadenopathy
- Unexplained pathologic bone fractures, osteopenia, osteoporosis, or osteosclerosis

(See 'Evaluation of common presentations' below.)

A simple bone marrow biopsy with histologic studies is less likely to be diagnostic of clonal mast cell disease in patients with serum tryptase levels <20 ng/mL. These patients should be offered referral to a mast cell disease research center with expertise in diagnosing mastocytosis, since pathognomonic clustering of mast cells may be absent in these patients [1].

http://www.uptodate.com/contents/evaluation-and-diagnosis-of-mast...+enterocolitis&selectedTitle=1%7E1&view=print&displayedView=full
Infants and children — Bone marrow biopsy is not routinely performed in infants and children with CM, unless there are specific findings to suggest extracutaneous organ involvement [2]. These include unexplained peripheral blood abnormalities, hepatomegaly, splenomegaly, or lymphadenopathy. This is a different approach from that recommended for adults.

Rarely, cutaneous disease may first be diagnosed in adolescence. These patients are generally evaluated as childhood-onset mastocytosis, although they may have a higher likelihood of having SM when compared with children whose lesions start within the first two years of life. Bone marrow evaluation for progression of disease to adult forms is indicated if skin lesions do not begin to regress or serum tryptase levels remain above the normal range (usually greater than 15 ng/mL) after puberty [2].

The signs and symptoms of the different types of SM are presented elsewhere. (See "Mastocytosis (cutaneous and systemic): Epidemiology, pathogenesis, and clinical manifestations").

Bone marrow studies — The bone marrow examination includes an evaluation of the histology of the core sample and of aspirated cells. Mast cells within the bone marrow core biopsy specimen are identified by immunohistochemical staining with antibodies to tryptase and/or c-kit receptor. Stains to detect CD25 should be performed, as mast cells in mastocytosis have pathologic expression of CD25. CD25 staining can be done in histopathology sections in most hospital pathology labs in formalin fixed bone marrow tissue. Metachromatic stains such as Giemsa or toluidine blue may fail to stain mast cells in the bone marrow core sections, as fixation and decalcification of the specimen can interfere with these stains. In addition, degranulated mast cells may lose their metachromatic staining properties.

A sample from the bone marrow aspirate should be examined for morphologically abnormal mast cells (eg, spindle-shaped, hypogranular forms) and submitted for flow cytometric (FACS) analysis of mast cells. Mast cells are rare events in FACS evaluation of bone marrow (generally less than 0.1 percent of cells) and are identified by high expression of CD117 (c-kit receptor). Acquisition of at least one million cell events is preferred to capture enough mast cells.

Expression of CD2 and CD25 should be assessed [3]. (See 'Flow cytometry' below.)

Analysis for KIT mutations should be performed. D816V KIT mutational analysis of bone marrow aspirates is commercially available in the United States, and it is also performed at several academic centers [1].

In patients with leukocytosis, eosinophilia, or both, examination for BCR/ABL and FIP1L1-PDGFRA fusion genes, as well as routine karyotyping, should be performed [4]. (See "Clinical manifestations, pathophysiology, and diagnosis of the hypereosinophilic syndromes", section on 'Myeloproliferative HES variants'.)

Evaluation of common presentations — Some authorities have suggested the following practical guide to evaluation based upon age and clinical presentation [4,5].

Urticaria pigmentosa in a child — In a child with skin lesions consistent with UP, initial evaluation includes the inspection of skin lesions, elicitation of Darier's sign, and the laboratories listed previously. (See 'Initial approach to the patient' above.)

A punch biopsy of the skin may be performed to confirm the diagnosis. Bone marrow examination is not necessary in children unless indicated by blood count or peripheral smear abnormalities, or other signs of an aggressive subtype (such as organomegaly, osteolyses, or others) [6].

Adults — Adults may present in several different ways.

Urticaria pigmentosa in an adult — All adults with UP-like skin lesions should undergo a bone marrow examination, in addition to skin biopsy and the basic laboratories mentioned previously, as systemic disease is present in most adult patients [4]. A serum tryptase level, complete blood count with differential, and liver function tests should
also be checked.

**Symptoms related to mast cell mediators, without skin lesions** — In patients with this presentation, basic laboratories mentioned previously and serum tryptase levels should be drawn. If tryptase levels are >20 ng/mL, a bone marrow examination should be considered.

**Unexplained severe allergic or anaphylactic reaction** — A serum tryptase level should be drawn for a patient presenting with unexplained allergic or anaphylactic-like reactions, particularly to a hymenoptera sting (regardless of whether skin testing to hymenoptera venom is positive or negative for IgE-mediated allergy). Anaphylactic reactions without hives should also raise the suspicion for SM. If the tryptase is greater than 20 ng/mL, a repeat serum tryptase and the basic studies mentioned above should be performed a few weeks later. If this repeat level is also greater than 20 ng/mL, a bone marrow examination should be pursued.

Some experts recommend a bone marrow biopsy in all patients presenting with recurrent unexplained hypotensive anaphylactic episodes regardless of tryptase levels, as a subset of these patients may have clonal mast cell disease [7]. (See ‘Differential diagnosis’ below.)

In addition, patients with unexplained anaphylaxis should undergo a thorough allergy evaluation, including skin testing and in vitro testing for allergen-specific IgE based on history. Skin testing in patients with CM and SM has been reported to be safe and reliable, although it should not be performed on lesional skin [8] (see "Idiopathic anaphylaxis"). It should be noted that some of these patients may be on scheduled antihistamines which would interfere with skin testing, but antihistamines should not be discontinued for the sole purpose of skin testing unless it is determined to be safe by an allergy specialist.

**LABORATORY FINDINGS**

Cutaneous forms of disease

**Laboratory results** — The complete blood count and differential are typically normal in cutaneous forms of mastocytosis, although a mild eosinophilia is sometimes noted. Liver function tests should be normal. The sedimentation rate is usually normal, although it may be slightly elevated if extensive areas of skin are affected. Serum tryptase and urinary histamine are usually normal, although they may be elevated when the skin is diffusely involved, such as in bullous forms of diffuse cutaneous mastocytosis (CM) [9-11].

**Histopathology of skin** — Skin biopsy establishes the diagnosis of CM but does not specify the category (which is determined clinically) or provide information about the risk of systemic disease [12,13]. There are four patterns of mast cell infiltrates that are observed in CM, which only partially correlate with the type of clinical lesion [14]:

- Perivascular infiltrates in the papillary and upper dermis are increased
- Sheet-like infiltrates in the papillary body and upper reticular dermis
- Interstitial infiltrates
- Nodular infiltrates

The phenotype of these mast cells is MCtc (tryptase/chymase/carboxypeptidase A3 positive), which is also the predominant mast cell of normal skin [15]. Mast cells in lesions of urticaria pigmentosa (UP) may have irregular shapes, sometimes with bilobated nuclei. On electron microscopy, they display a “scroll poor” phenotype with gratings and lattices. Other infiltrating cells may include eosinophils. (See "Mast cells: Development, identification, and physiologic roles" and "Mast cell derived mediators".)

It should be noted that mast cell numbers can be found increased in other inflammatory and neoplastic conditions of the skin, such as dermatofibromas, psoriasis, atopic dermatitis, etc. However, these disorders are also associated with additional characteristic pathologic changes in the skin. Likewise, biopsies findings alone, without the characteristic skin
lesions of various forms of CM, are not sufficient for diagnosis of CM. For example, the diagnosis of telangiectasia macularis eruptiva perstans (TMEP) should NOT be based on the findings in a skin biopsy alone without observation of the physical lesion, as mast cells can be found around blood vessels in healthy or inflamed skin.

**Systemic forms of disease** — Biochemical markers of mast cell activation and biopsy findings of increased mast cell infiltration in bone marrow are common abnormalities in patients with systemic mastocytosis (SM). Abnormalities suggestive of organ dysfunction, such as liver and gastrointestinal disease, may also be seen among those with significant extracutaneous disease.

**Serum tryptase** — Tryptase is a protease produced predominantly in mast cells, although a small amount is made by basophils and myeloid precursors as well. The presence of elevated serum concentrations of tryptase is one of the minor criteria for the diagnosis of mastocytosis [16]. (See 'Diagnosis' below.)

Tryptase measurements are useful in distinguishing mastocytosis from mast cell activation (table 1):

- **Total tryptase** - Total serum tryptase can be measured with a commercially available assay (ImmunoCAP tryptase, Phadia: Uppsala, Sweden), which is performed at many laboratories. Total tryptase is a measurement of both mature, active forms of tryptase, and immature, inactive forms (protryptases). Baseline tryptase is made up of immature (pro) tryptases that are constitutively secreted outside of the mast cell.

  Normal levels are between 1 and 11.4 ng/mL (some laboratories consider 15 ng/mL to be the upper limit of normal) (table 1). SM should be strongly suspected in patients with baseline levels of total tryptase greater than 20 ng/mL on at least two occasions [17].

- **Mature tryptase** - Mature tryptase is stored in mast cell granules and is elevated in serum in mast cell activation. An assay for mature (beta-) tryptase is presently performed only at Virginia Commonwealth University (Richmond, Virginia) [18]. The serum level of mature tryptase in healthy blood donors is less than 1 ng/mL. Levels of mature tryptase rise above 1 ng/mL with mast cell activation and systemic anaphylaxis reaching a peak approximately one hour after the event and generally returning to baseline after four hours. Mature tryptase levels are usually normal in patients with SM, unless they have just experienced an episode of massive mast cell activation. Measurement of mature tryptase is not required to make the diagnosis of mastocytosis, although it allows for an estimate of the total to mature ratio (table 1).

- **Ratio of total to mature tryptase** - If both measurements are available, the ratio of total to mature tryptase can be calculated. In healthy individuals without mastocytosis, the ratio is normally <20 [19]. In patients with SM this ratio is >20 (table 1).

During an acute anaphylactic event (in a patient without SM), mature tryptase rises and, if sufficiently high, can result in elevations of total tryptase. Mature tryptase levels >1 ng/mL, total tryptase levels >11 ng/mL, and a ratio of total to mature of <10 are each consistent with systemic anaphylaxis (table 1). The interpretation of tryptase levels in patients with suspected anaphylaxis is reviewed in detail separately. (See "Laboratory tests to support the clinical diagnosis of anaphylaxis".)

The absolute level of total tryptase does **not** predict the category of mastocytosis [19]. Aggressive mastocytosis and mastocytosis associated with hematological malignancies can have similar elevations of tryptase as indolent systemic mastocytosis (ISM). However, mast cell leukemia (MCL) is generally associated with extremely elevated tryptase levels, sometimes up to range of >1000 ng/mL. In general, there is a good correlation between an elevated total tryptase level and a positive bone marrow biopsy.

Tryptase elevations can also be detected in conditions other than mastocytosis, including patients with myeloproliferative or myelodysplastic disease, chronic renal or liver failure, and chronic eosinophilic leukemia.Persistently high tryptase was reported in one individual with no other criteria for mastocytosis [20]. This was attributed to the presence of human
anti-mouse antibodies that interfered with the immunoassay used to detect tryptase, which utilizes mouse monoclonal antibodies. Human anti-animal antibodies can be found in people who have received mouse monoclonal antibodies for imaging and therapeutic purposes, have occupational (farm or laboratory) or domestic animal exposure, or ingest cow's milk [21,22]. Another report described a significant association between the presence of IgM rheumatoid factor and heterophilic antibodies interfering with tryptase immunoassay, also resulting in falsely elevated tryptase levels [23].

**Urinary histamine** — The measurement of histamine or its metabolites in a 24-hour urine collection has been used in the diagnosis of SM, particularly prior to the availability of tryptase measurements [24]. Levels of urinary histamine are elevated in adults with SM. A urinary histamine concentration of up to 30 ng/mL is considered normal, although laboratories may utilize different units. Levels of urinary histamine can be found elevated in adults with SM.

Urinary histamine measurements can be affected by diet and urinary tract flora. Urinary histamine metabolites, such as N-methylhistamine, provide a more accurate assessment, but are neither more sensitive nor specific than serum tryptase levels [25]. In addition, increased histamine metabolite levels in urine obtained during a symptomatic episode, such as flushing or syncope, does not distinguish between anaphylaxis and SM.

**Bone marrow findings** — In healthy individuals, bone marrow mast cells represent less than 1 percent of all nucleated cells and have a morphology similar to mature mast cells in normal tissues [26]. Normal bone marrow mast cells are round cells with small nuclei and granulated cytoplasm that stains with metachromatic dyes. Protease stains indicate that these cells are of the MCtc phenotype, expressing tryptase and chymase and carboxypeptidase A3 [27].

The bone marrow in patients with SM ranges from normocellular to markedly hypercellular [28,29]. The clinical significance of the marrow burden of mast cells is unclear, but advanced forms of disease, such as aggressive SM and MCL, are associated with extensive bone marrow infiltration.

Among those with SM, frequently observed atypical mast cells have a spindle or fusiform shape, oval nuclei that are eccentric, hypogranular cytoplasm with focal accumulation of granules with or without granule fusion, and a high ratio nucleus:cytoplasm [28]. Multifocal aggregates of such spindle-shaped mast cells that contain at least 15 mast cells per aggregate are diagnostic for SM. Smaller aggregates with round mast cells of normal morphology as well as diffuse increases can also be found (figure 1 and picture 3).

The typical phenotype in SM is a mastocytosis positive for CD117, CD25, tryptase, and chymase [30]. Localization is predominantly paratrabecular and perivascular with thickened bony trabeculae, although interstitial infiltrates are not uncommon. Bone marrow mast cells can be very immature and hypogranulated and only recognizable by specific tryptase staining, rather than metachromatic stains, such as Giemsa or toluidine blue. Morphologically immature (multilobated or clefted nuclei, hypogranulated) bone marrow mast cells comprising more than 20 percent of cells in a nonspicular area of the bone marrow smear is diagnostic for MCL [28,31].

Bone marrow blood, collected at the time of bone marrow biopsy, may show elevated tryptase levels [15]. This was reported in one small study of seven patients, although the technique requires further validation, and its diagnostic utility has not been verified.

**Histologic evaluation of additional organs** — Histologic evaluation of organs other than bone marrow is generally not recommended for diagnosis of SM as bone marrow is almost always involved and the pathologic significance of increased mast cells in other tissues have not been carefully studied. Interpretation of gastrointestinal tract biopsies is problematic because mast cells are normally abundant in these tissues and so additional increases in normal mast cell concentration or the presence of aggregates are difficult to appreciate [32].

Exceptions to this include the following:

- In a minority of cases, extracutaneous and extramedullary organs are examined because of enlargement or dysfunction [33]. Multifocal aggregates of spindle-shaped mast cells can be found that are similar to those in the
bone marrow.

- Staining of the gastrointestinal mast cells for CD25 may be helpful when bone marrow sampling is not possible [34].

**KIT mutational analysis** — All patients with SM should undergo a mutational analysis of KIT, particularly for the presence of Asp816Val mutation. This analysis can be performed on peripheral white blood cells, bone marrow, or cells from skin or other organs. However, bone marrow lesional tissue yields the most sensitive results. Analysis of the peripheral blood is the least sensitive, as the mutation generally becomes detectable in peripheral blood in advanced forms of disease with multilineage involvement.

When appropriate tissues are analyzed, the D816V c-kit mutation is identified in more than 90 percent of patients with SM [35]. In addition to diagnostic information, this may aid in determining therapy.

**Flow cytometry** — Mast cells from patients with SM express the surface markers, CD2 (LFA-2) and CD25 (IL-2 receptor alpha chain), distinguishing them from normal or reactive mast cells, which display neither marker [4,36]. The expression of one or both of these markers is a minor criterion for the diagnosis (see 'Diagnosis' below). Mast cells can be identified in bone marrow aspirates as a CD117 high, IgE+ population [3,36,37]. In cases where bone marrow aspirate is not available for flow cytometry, immunohistochemical staining for CD25 may be performed in serial core biopsy sections.

**Other studies** — Additional abnormalities may be as detected by radiography, computed tomography (CT) scan, magnetic resonance imaging (MRI), bone scan, gastrointestinal studies, and/or endoscopy, depending upon the extent of organ infiltration and the symptoms of the patient.

The diagnosis of clonal mast cell disorders based on biopsies other than bone marrow should generally be avoided.

- **Gastrointestinal biopsies** - Increased mast cell numbers can be found in gastrointestinal tract biopsies from patients with inflammatory bowel diseases and bacterial and parasitic infections, as well as in some patients with systemic mast cell disease. There are conflicting reports about the gastrointestinal mast cell density in patients with SM. One study found greater than 20 mast cells per high-power field in a subset of patients with chronic intractable diarrhea without evidence of mastocytosis or other inflammatory bowel disease [38]. These patients were termed as having mastocytic enterocolitis. These findings need to be verified in future studies. Another study found decreased numbers of mast cells in gastric and duodenal biopsies of patients with SM when compared with controls [32], while other studies reported increased numbers [36]. Thus, increased mast cell numbers in gastrointestinal biopsies should not be interpreted as diagnostic of a systemic mast cell disease. Patients with gastrointestinal symptoms are sometimes inappropriately diagnosed with either SM or "mast cell activation syndrome" (MCAS) based upon gastrointestinal biopsies. However, expression of CD25 in gastrointestinal mast cells is a useful diagnostic marker for presence of SM.

- **Bladder wall biopsies** - Patients with the diagnosis of "mast cell activation syndrome" (MCAS) sometimes have a variety of waxing and waning symptoms affecting multiple systems. Symptoms similar to interstitial cystitis may be observed in some patients. Increased numbers of degranulated mast cells in bladder biopsies suggest that mast cells contribute to some of the pathology of this disorder [39]. However, a diagnosis of interstitial cystitis does not generally raise suspicion for the presence of SM. In some patients, improvement of symptoms with drugs targeting mast cell mediators (such as H1 and H2 antihistamines, cromolyn, leukotriene antagonists) are considered as further supporting evidence of mast cell involvement in disease process. However, these findings are nonspecific and do not support the diagnosis of a primary systemic mast cell disorder.

**DIAGNOSIS**

**Cutaneous mastocytosis** — The diagnosis of cutaneous mastocytosis (CM) is based upon the presence of suggestive...
signs and symptoms, combined with characteristic cutaneous lesions and findings on skin biopsy (table 2). (See ‘Skin biopsy’ above.)

Systemic mastocytosis — According to the World Health Organization's (WHO) diagnostic criteria, the definitive diagnosis of systemic mastocytosis (SM) requires either the presence of one major and one minor criteria OR three minor criteria (table 2) [31]:

Major criterion — The major criterion is the presence in bone marrow or other extracutaneous organs of multifocal dense aggregates of greater than 15 mast cells as detected with tryptase or other special stains.

Minor criteria — Four minor criteria have been defined:

- Atypical morphology or spindle shapes in >25 percent of the mast cells in bone marrow sections, bone marrow aspirate, or other extracutaneous tissues.
- Mutational analysis of KIT showing a codon 816 mutation (eg, Asp816Val) in bone marrow, blood, or extracutaneous organs.
- Bone marrow or other extracutaneous mast cells expressing the surface markers CD2, CD25, or both.
- Serum tryptase levels (when the patient is in a baseline state) >20 ng/mL. Values >11.4 ng/mL are considered elevated in most diagnostic laboratories; however, the WHO criterion is currently defined as a value >20 ng/mL. Of note, the serum tryptase criterion does not apply to patients with an associated hematologic clonal nonmast cell lineage disease (AHNMD).

Bone marrow biopsy is the optimal means of pursuing the diagnosis of SM. Other organs (such as spleen or lymph nodes) are occasionally used as a source of mast cells if they have been removed as part of evaluation or treatment.

DIFFERENTIAL DIAGNOSIS — Mastocytosis can be confused either clinically or histologically with a variety of disorders, although application of the World Health Organization's (WHO) criteria to pathologic samples confirms or rules out the diagnosis of systemic mastocytosis (SM).

Disorders with similar clinical manifestations — Mastocytosis is a histopathologic diagnosis and should not be based solely on clinical presentation. The ability to distinguish SM from illnesses with similar clinical manifestations is principally based upon the presence or absence of elevated levels of biochemical mediators of mast cell activation, including tryptase and histamine, the lack of skin lesions typical for SM, and a definitive histologic diagnosis of SM:

- Monoclonal mast cell activation syndrome — The term monoclonal mast cell activation syndrome (MMAS) has been accepted by a consensus panel as appropriate for patients who experience episodes of mast cell activation symptoms, such as recurrent flushing, gastrointestinal cramping, and hypotension and meet one or two of the minor diagnostic criteria for SM (eg, c-kit D816V or aberrant CD25 expression on mast cells), but do not fully meet diagnostic criteria for SM. (See ‘Minor criteria’ above.)

Patients with MMAS may present with hypotensive reactions to Hymenoptera stings and demonstrate baseline serum tryptase values that are normal or mildly increased. Bone marrow findings do not meet criteria for SM, although some cells express the aberrant markers CD2 and CD25 and/or KIT mutations. MMAS is reviewed in greater detail separately. (See "Mast cell activation disorders".)

- Anaphylaxis — Clinical criteria for the diagnosis of anaphylaxis have been defined (table 3). Patients with anaphylaxis may have elevations of serum beta (mature) tryptase during (or for several hours after) acute events. In contrast, patients with SM have persistent elevations in total tryptase in the baseline state. Patients with Hymenoptera anaphylaxis and elevated random tryptase should be evaluated for SM, regardless of the results of testing for Hymenoptera sensitization. Idiopathic anaphylaxis (IA) is a diagnosis of exclusion. (See "Idiopathic
Finally, patients should exhibit a favorable clinical response to medications that counteract mast cell mediators, including H1 and H2 antihistamines, antileukotriene medications, or oral cromolyn sodium.

The clinical and laboratory findings of SM, MMAS, MCAS, and IA are summarized in the table (table 4). MCAS is reviewed in more detail separately. (See "Mast cell activation disorders").

The next group of disorders described below, which can have some clinical features similar to mastocytosis, do not involve mast cell activation. Therefore, serum tryptase and urinary histamine are not elevated:

- **Mast cell activation syndrome** — Mast cell activation syndrome (MCAS) is a term proposed to describe an idiopathic disorder in which patients present with recurrent episodes of signs and symptoms that are consistent with mast cell activation and affect at least two organ systems (ie, cutaneous, gastrointestinal, cardiovascular, respiratory, or naso-ocular) [40]. Of note, the signs and symptoms should **not** fulfill criteria for anaphylaxis (table 3), nor should there be any KIT mutations or mast cell CD25 expression. If the criteria for anaphylaxis are met, then the diagnosis of IA is more appropriate.

In addition, elevations in mast cell mediators in serum or urine should be documented as follows:

- In patients with a baseline serum total tryptase ≥15 ng/mL, a further increase in serum tryptase, 24-hour urine N-methylhistamine or prostaglandin D₂ or its metabolite 11-beta-prostaglandin F₂ should be demonstrated on at least one occasion during a symptomatic period.

- In patients with a baseline serum tryptase <15 ng/mL, an increase in the same mediators should be demonstrated on at least two occasions during symptomatic periods.

Finally, patients should exhibit a favorable clinical response to medications that counteract mast cell mediators, including H1 and H2 antihistamines, antileukotriene medications, or oral cromolyn sodium.

The next group of disorders described below, which can have some clinical features similar to mastocytosis, do not involve mast cell activation. Therefore, serum tryptase and urinary histamine are not elevated:

- **Hereditary/acquired angioedema** - Patients with hereditary or acquired angioedema due to deficiency of C1 inhibitor present with episodes of angioedema (generally painful) affecting the skin, larynx, and/or walls of the bowel. In contrast, laryngeal edema is unusual in mastocytosis and C1 inhibitor and complement studies are typically within normal range in mastocytosis. (See "An overview of angioedema: Clinical features, diagnosis, and management").

- **Carcinoid syndrome** - The presence of episodic flushing and diarrhea may raise suspicion for mastocytosis among patients with the carcinoid syndrome. Elevations of 24-hour urine 5-HIAA are indicative of carcinoid syndrome, whereas this mediator is normal in mastocytosis. (See "Diagnosis of the carcinoid syndrome and tumor localization").

- **Pheochromocytoma** - Patients with pheochromocytoma may present with flushing and paroxysmal episodes of hypertension, whereas patients with mastocytosis generally develop hypotension during an acute mast cell degranulation episode. (See "Clinical presentation and diagnosis of pheochromocytoma").

- **Metastatic disease to bone** - Bone lesions of SM are frequently misinterpreted radiographically as metastatic lesions to bone; however, elevated serum tryptase and urinary histamine are absent with malignancy. Thus, histopathologic diagnosis is required to differentiate between these two disorders.

- **Vasoactive intestinal peptide-secreting tumors** - Symptoms found in both SM and vasoactive intestinal peptide (VIP)-secreting tumors include flushing episodes and particularly diarrhea. VIP-secreting tumors are associated with increased levels of VIP. (See "The VIPoma syndrome").

- **Zollinger-Ellison syndrome** - A significant number of patients with the Zollinger-Ellison syndrome present with diarrhea. Some affected individuals may also have metastatic disease to bone. However, Zollinger-Ellison syndrome is not associated with elevated levels of histamine or tryptase. (See "Clinical manifestations and
Disorders with similar bone marrow manifestations — A few disorders have increased and/or aberrantly shaped mast cells similar to findings in the bone marrow as observed in patients with SM. These are principally chronic eosinophilic leukemia (CEL), primary myelofibrosis, and reactive mastocytosis, which are distinguished from mastocytosis by differences on bone marrow biopsy as well as the presence or absence of characteristic clinical and laboratory features.

- **Chronic eosinophilic leukemia or myeloproliferative variant of hypereosinophilic syndrome** - These disorders are characterized by a modest elevation in serum tryptase and atypical spindle-shaped mast cells expressing surface CD25. However, molecular diagnostic studies reveal the presence of FIP1L1-PDGFRA fusion instead of a D816V KIT mutation. The typical patient is a male without urticaria pigmentosa (UP) and a hypercellular (myeloproliferative) bone marrow with elevated serum vitamin B12 levels. This is a stem cell disorder affecting multiple hematopoietic lineages including the mast cell, but the clinical disease manifestations are due to eosinophil-related pathology rather than increased mast cells. Some patients may meet the diagnostic criteria of both disorders (SM associated with CEL). These patients respond well to imatinib, whereas patients with typical mastocytosis and D816V c-kit mutations do not. (See "Clinical manifestations, pathophysiology, and diagnosis of the hypereosinophilic syndromes" and "Treatment of the hypereosinophilic syndromes".)

- **Primary myelofibrosis** - Bone marrow biopsy in patients with primary myelofibrosis typically reveals extensive fibrosis, which may be accompanied by spindle-shaped mast cells, a finding that can also be observed with mastocytosis in the setting of extensive mast cell infiltration. However, mast cell increase is usually diffuse and interstitial rather than forming clusters. Also, mast cells in myelofibrosis lack pathologic CD25 expression and c-kit D816V mutation. (See "Clinical manifestations and diagnosis of primary myelofibrosis".)

- **Reactive mastocytosis** - Reactive mastocytosis in tissues and bone marrow can be seen in patients with solid tumors, such as breast cancer, Hodgkin lymphoma, and in diseases variably associated with increased expression of stem cell factor (eg, aplastic anemia and some hematologic, soft tissue, and gastrointestinal neoplasms). Reactive mast cells generally have a mature appearance (round in shape and fully granulated) and lack significant clustering and aberrant surface expression of CD25 and CD2 and KIT mutations.

**Determining the category of systemic mastocytosis** — Once the diagnosis of systemic mastocytosis (SM) has been made, the category of SM should be determined. Each category is distinguished by various features (table 5). To establish the category of SM present, a bone marrow biopsy, serum tryptase levels, complete blood counts with differential, and liver function tests are recommended for all patients. Depending on the clinical presentation, the following additional studies may be indicated:

- Coagulation studies (prothrombin time, activated partial thromboplastin time)
- Gastrointestinal endoscopy with biopsies
- Bone radiography to evaluate bone pain and assess for pathologic fractures
- Total body radionuclide bone scan
- Bone densitometry to evaluate for bone loss, since mastocytosis is a risk factor for osteoporosis
- Abdominal ultrasonography or computed tomography (CT) scan to evaluate for splenomegaly, hepatomegaly, and lymphadenopathy
- KIT mutational analysis (generally performed at the time of bone marrow biopsy, and preferably on bone marrow aspirate cells)
- Cytogenetic analysis in patients with suspected co-existent hematologic disease
- FISH for CHIC2 deletion in patients with suspected co-existent chronic eosinophilic leukemia (CEL)/myeloproliferative hypereosinophilic syndrome (HES) (see "Clinical manifestations, pathophysiology, and
In addition, the presence of B and C findings should be noted.

**B findings** — B findings refer to organ enlargement without organ dysfunction and may be observed in patients with indolent systemic mastocytosis (ISM) with high mast cell burden. Patients with smoldering ISM have a high mast cell burden and extensive bone marrow infiltration by mast cells, but no features of aggressive disease or an associated hematologic nonmast cell clonal disease [4]. B findings include the following (table 5) [41]:

- Infiltration of bone marrow such that mast cells comprise >30 percent of cells and serum tryptase is >200 ng/mL.
- Hypercellular bone marrow with loss of fat cells or discrete signs of myelodysplasia or myeloproliferation (but insufficient to diagnose myelodysplastic syndrome [MDS] or unclassifiable myeloproliferative neoplasms [MPD]), normal blood counts, or slight persisting deviation without progression.
- Palpable hepatomegaly without ascites or other signs of organ impairment and/or palpable lymphadenopathy or visceral node enlargement (<2 cm) found on ultrasound or CT and/or palpable splenomegaly without hypersplenism.

**C findings** — C findings denote organ-function impairment due to excessive mast cell infiltration and are associated with aggressive disease and a poorer prognosis. C findings are present in aggressive systemic mastocytosis (ASM). In addition, they may be observed in mast cell leukemia (MCL). C findings include (table 5) [41]:

- Cytopenias due to bone marrow infiltration, as defined by one or more of the following: absolute neutrophil count <1000 cells/mcL, hemoglobin <10 g/dL, platelets <100,000 mcL [42]. In patients with systemic mastocytosis with associated hematologic clonal nonmast cell lineage disease (SM-AHNMD), it may be difficult to determine whether the cytopenias are due to mastocytosis or the associated hematologic disorder.
- Palpable hepatomegaly with ascites, elevated liver function tests (eg, hepatic enzymes, alkaline phosphatase, and lactate dehydrogenase), impaired synthesis of albumin and coagulation factors, and/or portal hypertension.
- Palpable splenomegaly with hypersplenism (ie, nonimmune hemolytic anemia and other hematologic abnormalities) (see "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism").
- Malabsorption due to mast cell infiltration of the intestinal tract with hypoalbuminemia and weight loss (see "Clinical features and diagnosis of malabsorption").
- Bone lesions with large osteolyses and/or severe osteoporosis with spontaneous and/or pathologic fractures.

**Indolent systemic mastocytosis** — Most patients with ISM are adults or children over 10 years of age [4,43]. ISM is the most prevalent form of SM in adults [44,45]. In the majority of cases of ISM, urticaria pigmentosa (UP) lesions are present, and the diagnosis is made by histologic examination of the skin and bone marrow [46]. The KIT mutation Asp816Val is detected in skin lesions and bone marrow mast cells, and rarely in peripheral blood cells [47].

The presence of B findings defines the "smoldering" subtype of ISM [4]. Although mast cell infiltrates can be detected in various organs (including liver, spleen, and gastrointestinal tract), the clinical course is generally indolent. However, these patients should be followed for progression to a more aggressive form of disease.

**Systemic mastocytosis with associated clonal hematologic nonmast cell lineage disorder** — Patients with SM-AHNMD fulfill clinical criteria for SM and another hematologic syndrome or neoplasia according to the World Health Organization's (WHO) criteria [43,48].

Unlike those with ISM, only 50 percent of patients with SM-AHNMD have UP-like skin lesions. As a result, the diagnosis
of mastocytosis may be missed or delayed. (See 'Differential diagnosis' above.)

The most commonly associated hematologic disorders are myeloproliferative or myelodysplastic diseases, although lymphoproliferative diseases, such as myeloma and lymphomas and secondary acute leukemias, have also been reported. Most of these patients present with activating Asp816Val KIT mutations in the peripheral blood, indicating a multipotential hematopoietic clonal nature of the SM [49,50]. Rare cases of SM associated with myeloproliferative disorders exhibiting both c-kit D816V and JAK2 V617F mutations have been reported. Among the disorders that have been reported in association with SM are the following [28]:

- Chronic myelomonocytic leukemia (CMML)
- Myelodysplastic syndromes (MDS)
- Unclassifiable myeloproliferative neoplasms (MPD)
- Hypereosinophilic syndrome
- Chronic eosinophilic leukemia (CEL)
- Acute myeloid leukemia (especially that associated with t(8:21)(q22;q22))
- Plasma cell myeloma
- Hairy cell leukemia
- Polycythemia vera
- Hodgkin's and non-Hodgkin lymphoma
- Primary thrombocytopenia or thrombocytopenia
- Chronic myeloid leukemia (CML)

(See "Clinical manifestations and diagnosis of the myelodysplastic syndromes" and "Overview of the myeloproliferative neoplasms" and "Clinical manifestations, pathologic features, and diagnosis of acute promyelocytic leukemia in adults".)

Aggressive systemic mastocytosis — ASM, a clinically severe form of SM, occurs in a minority of patients [33]. This category of SM is characterized by one or more C findings (ie, organ-function impairment due to excessive mast cell mass) [51]. (See 'C findings' above.)

UP lesions can be present or absent. Mast cells in the bone marrow biopsy typically occupy >20 percent of the marrow space, but are typically less than 20 percent of nucleated cells in the aspirate smear, which distinguishes ASM from MCL. Signs of dysplasia and myeloproliferation can be found, but do not fulfill criteria for hematologic malignancy.

Tryptase levels are invariably increased. Mutations of c-kit kinase domain may be present, including the most common Asp816Val mutation [52].

A variant of ASM can also present with lymphadenopathic mastocytosis with blood and/or tissue eosinophilia.

Mast cell leukemia — MCL is the rarest and most aggressive category of SM. It is characterized by more than 10 percent circulating mast cells in peripheral blood or more than 20 percent mast cells in the bone marrow aspirate with atypical features. In the bone marrow, cells can be very immature and hypogranulated with blast-like morphology and high nucleus:cytoplasm ratios, and may contain mitotic figures. For the purpose of diagnosing MCL, the percentage of mast cells should be determined in a nonspicular part of the bone marrow aspirate smear and not in bone marrow biopsy sections.

Mast cells are not found in peripheral blood in healthy individuals and in patients with ISM. Therefore, the number of circulating mast cells in the peripheral blood may help distinguish MCL from other categories of mastocytosis [53,54]. The number of circulating mast cells in MCL can vary considerably. As an example, an "aleukemic" variant of MCL is characterized by less than 10 percent circulating mast cells in the presence of >20 percent immature mast cells in bone marrow aspirate smears.

Typically, although UP lesions are absent, initial clinical presentation of the disease cannot be distinguished from the other categories. Signs and symptoms include flushing, hypotension, and diarrhea. Plasma tryptase levels are usually extremely high. Mutations of the activation domain of KIT at codon 816 can be observed [55]. This mutation was originally described in a mast cell line derived from a patient who died of MCL [56].

Progression to multiple organ failure with weight loss, bone pain, and organomegaly develops over months.

**MAST CELL SARCOMA** — Mast cell sarcoma is a rare disorder, with few well-documented cases [57,58]. Subsequent evolution to mast cell leukemia (MCL) may occur. The sarcoma is a locally destructive lesion without systemic (bone marrow) involvement at the time of the diagnosis. Atypical sarcomatous mast cells have been reported within the larynx, colon, brain, skin, and mucosal tissues.

**EXTRACUTANEOUS MASTOCYTOMAS** — Extracutaneous mastocytomas are also rare, and are characterized by accumulation of mature mast cells in an organ other than the skin, without aggressive features. Most reported cases were localized to the lung. In a report of a skull mastocytoma, significant bone destruction was induced by the mast cell mass [59]. Evolution of extracutaneous mastocytomas to mast cell sarcoma has not been described.

**SUMMARY** — Mastocytosis is a group of disorders caused by excessive mast cell proliferation. Mastocytosis limited to the skin is called cutaneous mastocytosis (CM), whereas mastocytosis involving extracutaneous tissues is called systemic mastocytosis (SM). (See 'Introduction' above.)

- The evaluation of a patient with suspected mastocytosis (cutaneous or systemic) begins by evaluation for signs and symptoms of systemic involvement, and a skin examination for suspicious lesions, such as urticaria pigmentosa (UP), a fixed and diffuse dermatitis composed of small, fixed, hyperpigmented macules that urticate or flush when rubbed (Darier's sign) ([picture 1](#)). In addition, a complete blood count with differential, liver function tests, and a serum tryptase should be obtained. (See 'Initial approach to the patient' above.)

- Patients with lesions consistent with CM should undergo a punch biopsy of skin lesions with specific histopathologic stains, if there is any doubt about the diagnosis. Skin biopsy findings in the context of the morphologic lesion are diagnostic of CM, but do not provide information about systemic involvement. (See 'Skin biopsy' above.)

- Bone marrow biopsy is not routinely performed in infants and children with CM, unless there are specific findings to suggest other organ involvement (eg, unexplained abnormalities on the complete blood count, hepatomegaly, splenomegaly, or lymphadenopathy). In contrast, adult patients with UP, an elevated serum tryptase level, or signs and symptoms of systemic involvement should undergo bone marrow biopsy and aspiration. (See 'Indications for bone marrow examination' above.)

- In CM, laboratories are typically normal and the diagnosis is confirmed by skin biopsy findings ([table 2](#)). (See 'Cutaneous forms of disease' above and 'Cutaneous mastocytosis' above.)

- In SM, abnormalities include characteristic bone marrow findings, a persistently elevated baseline total tryptase (>20 ng/mL) ([table 1](#)), and variable other findings of systemic involvement. (See 'Systemic forms of disease' above.)

- The diagnosis of SM requires either the presence of the major criterion and one of the minor criteria, OR three of the minor criteria (in the absence of the major criterion) ([table 2](#)). (See 'Diagnosis' above.)

- Once the diagnosis of SM has been established, further evaluation is performed to determine which of the categories of disease is present and whether there are B or C findings present ([table 5](#)). (See 'Determining the category of systemic mastocytosis' above.)
REFERENCES

1. Some centers with extensive experience in the United States include Brigham and Women's Hospital, the National Institutes of Health (NIH), Mayo Clinic, and MD Anderson Cancer Center.


18. The laboratory can be contacted at (804) 828-9685.


23. van Toorenenbergen AW, Hooijkaas H, Heerenbrink GK, Dufour-van den Goorbergh DM. Heterophilic antibody...
47. Longley BJ, Metcalfe DD. A proposed classification of mastocytosis incorporating molecular genetics. Hematol


Topic 4784 Version 12.0
Urticaria pigmentosa

Urticaria pigmentosa lesions in an adult patient with cutaneous mastocytosis.


Graphic 63025 Version 3.0
Mastocytoma

Cutaneous mastocytomas on the hand of a child.


Graphic 76891 Version 3.0
# Mature and total tryptase levels in anaphylaxis and systemic mastocytosis

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Tryptase levels (ng/mL)</th>
<th>Total/mature tryptase ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Mature</td>
</tr>
<tr>
<td>Normal</td>
<td>1 to 11.4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Systemic anaphylaxis (acute)</td>
<td>&gt; baseline</td>
<td>&gt;1*</td>
</tr>
<tr>
<td>Systemic mastocytosis (nonacute)</td>
<td>&gt;20Δ</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

NA: not applicable.

* Acute total tryptase level >2 + (1.2 x patient’s baseline total tryptase level).
- Level related to clinical severity (hypotension), timing of sample collection in relation to onset of signs and symptoms, and nature of the anaphylactic stimulus.

Δ Reflects primarily the total body burden of mast cells when subject is in a non-anaphylactic state. A baseline total tryptase level >11.4 ng/mL should raise the possibility of an underlying clonal mast cell disorder (eg, systemic mastocytosis) or a primary mast cell activation disorder.
Bone marrow biopsy - systemic mastocytosis - tryptase staining

The bone marrow shows multifocal dense infiltrates (arrow) of greater than 15 mast cells. The abnormal-appearing, spindle-shaped mast cells are typically located near thickened bony trabeculae. Tryptase staining is positive.

Courtesy of Mariana C Castells, MD, PhD.

Graphic 78615 Version 2.0
Bone marrow biopsy from a patient with systemic mastocytosis

The mast cells stain for the presence of c-kit, the receptor for stem cell factor.

_Courtesy of Mariana C Castells, MD, PhD._

Graphic 69849 Version 3.0
### Diagnostic criteria for cutaneous and systemic mastocytosis

<table>
<thead>
<tr>
<th><strong>Cutaneous mastocytosis (CM)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin lesions demonstrating the typical clinical findings of urticaria pigmentosa/maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis or solitary mastocytoma, and typical histological infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy. In addition, a diagnostic prerequisite for the diagnosis of CM is the absence of features/criteria sufficient to establish the diagnosis of SM.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Systemic mastocytosis (SM)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>The diagnosis of SM can be made when the major criterion and one minor criterion or at least three minor criteria are present</td>
</tr>
</tbody>
</table>

**Major criterion:**

> Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)

**Minor criteria:**

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


Graphic 82827 Version 4.0
## Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any ONE of the following three criteria is fulfilled:

1. **Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)**

   **AND AT LEAST ONE OF THE FOLLOWING:**
   
   A. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   
   B. Reduced BP* or associated symptoms of end-organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)

2. **TWO OR MORE OF THE FOLLOWING that occur rapidly after exposure to a LIKELY allergen for that patient (minutes to several hours):**

   A. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   
   B. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
   
   C. Reduced BP* or associated symptoms (eg, hypotonia, collapse, syncope, incontinence)
   
   D. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. **Reduced BP* after exposure to a KNOWN allergen for that patient (minutes to several hours):**

   A. Infants and children - Low systolic BP (age specific)* or greater than 30 percent decrease in systolic BP
   
   B. Adults - Systolic BP of less than 90 mmHg or greater than 30 percent decrease from that person’s baseline

---

BP: blood pressure.

* Low systolic blood pressure for children is defined as:
  
  - Less than 70 mmHg from one month to one year,
  
  - Less than \((70 \text{ mmHg} + [2 \times \text{age}])\) from 1 to 10 years, and
  
  - Less than 90 mmHg from 11 to 17 years


Graphic 72225 Version 11.0
## Comparison of clinical and diagnostic features for systemic mastocytosis, mast cell activation syndromes, and idiopathic anaphylaxis

<table>
<thead>
<tr>
<th></th>
<th>Baseline tryptase*</th>
<th>Systemic mastocytosis</th>
<th>Monoclonal mast cell activation syndrome (MMAS)</th>
<th>Mast cell activation syndrome (MCAS)</th>
<th>Idiopathic anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-kit D816V</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Multifocal mast cell aggregates</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aberrant CD25</td>
<td>+/−</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Mediator-release symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypotensive episodes</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
<td>+/−</td>
</tr>
<tr>
<td>Urine N-MH or PGD&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Increased at baseline</td>
<td>Increased during symptoms</td>
<td>Increased during symptoms</td>
<td>Increased during symptoms</td>
<td></td>
</tr>
<tr>
<td>Response to antimediator therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
</tr>
</tbody>
</table>

N-MH: N-methylhistamine; PGD<sub>2</sub>: prostaglandin D2.

* Elevations in serum tryptase corresponding to symptoms (particularly hypotension) may be seen in all four disorders. Increases in tryptase greater than 1.2 x baseline value + 2 ng/mL are considered significant. For example, if a patient’s baseline total tryptase were 5 ng/mL, a value of 8 ng/mL would represent a significant increase.

Reproduced from: Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. J Allergy Clin Immunol 2010; 126:1099. Illustration used with the permission of Elsevier Inc. All rights reserved.

Graphic 74223 Version 9.0
## Diagnostic criteria of variant forms of systemic mastocytosis (SM)

| **Indolent systemic mastocytosis (ISM)** | Meets criteria for SM. No "C" findings (see below). No evidence of an associated nonmast cell lineage clonal hematological malignancy/disorder (AHNMD). In this variant, the mast cell burden is low and skin lesions are often present, to reflect the increasing numbers of patients diagnosed without skin lesions. |
| **Bone marrow mastocytosis** | As above (ISM) with bone marrow involvement, but no skin lesions. |
| **Smouldering systemic mastocytosis** | As above (ISM), but with two or more "B" findings, and no "C" findings. |

### Smouldering systemic mastocytosis with associated clonal hematological nonmast cell lineage disease (SM-AHNMD)

Meets criteria for SM and criteria for an associated clonal hematological nonmast cell lineage disorder, AHNMD (MDS, MPN, AML, lymphoma, or other hematological neoplasm that meets the criteria for a distinct entity in the WHO classification).

| **Aggressive systemic mastocytosis (ASM)** | Meets criteria for SM. One or more "C" findings. No evidence of mast cell leukaemia. Usually without skin lesions. |
| **Lymphadenopathic mastocytosis with eosinophilia** | Progressive lymphadenopathy with peripheral blood eosinophilia, often with extensive bone involvement, and hepatosplenomegaly, but usually without skin lesions. Cases with rearrangement of PDGFRA are excluded. |

| **Mast cell leukemia (MCL)** | Meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. Bone marrow aspirate smears show 20 percent or more mast cells. In typical MCL, mast cells account for 10 percent or more of peripheral blood white cells. Rare variant: aleukemic mast cell leukemia, as above, but <10 percent of white blood cells are mast cells. Usually without skin lesions. |
| **Mast cell sarcoma (MCS)** | Unifocal mast cell tumour. No evidence of SM. Destructive growth pattern. High-grade cytology. |


### "B" findings

1. Bone marrow biopsy showing >30 percent infiltration by mast cells (focal, dense aggregates)
1. Signs of dysplasia or myeloproliferation, in nonmast cell lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or only slightly abnormal blood counts.

2. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.

"C" findings

1. Bone marrow dysfunction manifested by one or more cytopenia (ANC <1.0 x 10^9/L, Hb <10 g/dL, or platelets <100 x 10^9/L), but no obvious nonmast cell hematopoietic malignancy.

2. Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension.

3. Skeletal involvement with large osteolytic lesions and/or pathological fractures.

4. Palpable splenomegaly with hypersplenism.

5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.


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