

# Mastocytosis

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## KEYWORDS

• Mast cell • Mastocytosis • KIT • Bone marrow • Skin • Urticaria

## KEY POINTS

- The pathologic proliferation of mast cells is a defining feature of mastocytosis.
- Cutaneous manifestations may occur alone or in association with systemic disease at any age.
- The most commonly affected site is the skin.
- Mastocytosis in children is usually limited to the skin and resolves by adulthood.
- Patients with systemic disease often have a somatic activating mutation in the KIT oncogene, which may direct the diagnosis and treatment.
- Treatment is primarily symptomatic for nonaggressive variants of mastocytosis.
- Patients with aggressive disease may benefit from cytoreductive therapies.

## INTRODUCTION

Mastocytosis is a disorder of increased mast cell proliferation, with both cutaneous and systemic manifestations. Clinical features of mastocytosis include flushing, pruritus, abdominal pain, diarrhea, hypotension, syncope, and musculoskeletal pain. These features are primarily the result of mast cell mediator release and infiltration into skin, gastrointestinal (GI) tract, liver, spleen, lymph nodes, and bone marrow. The skin is the most common site of involvement. Cutaneous disease manifestations include urticaria pigmentosa, diffuse cutaneous mastocytosis (DCM), mastocytoma, and telangiectasia macularis eruptiva perstans. Mastocytosis occurs in both children and adults, although children tend to primarily manifest cutaneous lesions. Most cases seem to be spontaneous. Inherited patterns of mastocytosis are unusual.

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Mastocytosis has been classified into disease variants, which are listed in **Box 1** according to a World Health Organization (WHO) consensus.<sup>1</sup> Children with cutaneous mastocytosis (CM) generally have resolution of symptoms by adulthood. In adults, cutaneous disease is usually accompanied by evidence of mastocytosis in other organ systems. Indolent systemic mastocytosis (ISM) (**Fig. 1**) is the least severe systemic variant, and patients with ISM or isolated CM are generally managed long-term with symptomatic therapies. Other forms with more severe manifestations carry a poorer prognosis and include systemic mastocytosis with an associated clonal, hematologic non-mast-cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL) and mast cell sarcoma. Of these forms, MCL, although rare, is the most aggressive and may be characterized by the presence of immature mast cells in peripheral blood.

## CAUSES AND PATHOGENESIS

### *Mast Cell Origin, Growth, and Development*

Human mast cells develop from CD34<sup>+</sup> pluripotent progenitor cells.<sup>2–5</sup> Committed bone marrow– derived mast cell progenitors enter the bloodstream, then migrate to peripheral tissue, where they mature and become terminally differentiated. Mature mast cells tend to reside in tissue close to blood vessels, nerves, and glandular structures. They are particularly numerous in the skin, GI tract, respiratory tract, and lymphoid tissue. Mast cells have cytoplasmic granules that contain histamine and a multitude of other inflammatory mediators. Mature mast cells are long lived and tend to have a limited ability to differentiate.<sup>6</sup> Mast cell survival is particularly dependent on the presence of stem cell factor (SCF) in the surrounding milieu.

Mast cells, as well as melanocytes, express KIT, a transmembrane tyrosine kinase receptor for SCF. The interaction between KIT and SCF seems to play an essential role in the development of mastocytosis.<sup>7</sup> Activating somatic mutations in *c-kit*, which encodes for KIT, have been detected in the bone marrow as well as skin and peripheral blood cells in patients with mastocytosis. The most common somatic mutation,

#### **Box 1**

#### **World Health Organization classification of mastocytosis**

##### CM

Urticaria pigmentosa = maculopapular CM

##### DCM

Mastocytoma of skin

##### ISM

Smoldering systemic mastocytosis

Isolated bone marrow mastocytosis

Systemic mastocytosis with associated clonal, hematologic non-mast-cell lineage disease

Aggressive systemic mastocytosis

Mast cell leukemia

Mast cell sarcoma

Extracutaneous mastocytoma

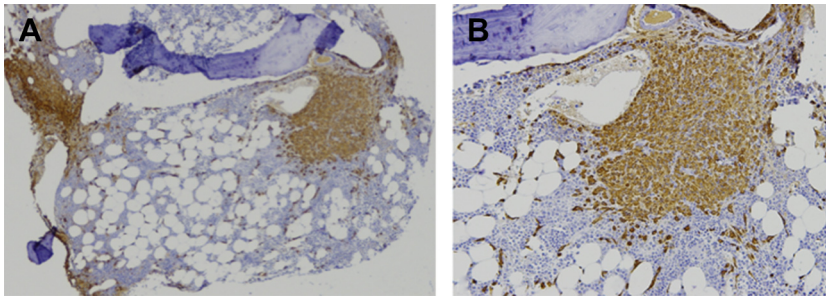


**Fig. 1.** Bone marrow histopathology in an adult with ISM. Mast cell aggregates shown by staining with tryptase in (A) ( $\times 40$ ) and (B) highlights the mast cell component of the aggregate and the prominent abnormal spindle-shaped mast cells ( $\times 100$ ).

Asp816Val (D816V), is located in catalytic domain of KIT and results in augmented mast cell proliferation and survival.<sup>8,9</sup> The D816V mutation is less common in children, especially in those with CM. Other c-kit mutations including V560G, D816Y, D816F, D816H, and E839K have been identified in mast cell lines, MCL, and pediatric mastocytosis.<sup>10,11</sup> Whether these are activating mutations or contribute to ligand-independent activation and suppression of apoptosis has not been fully elucidated. A subgroup of patients who present with hypereosinophilic syndrome have the FIP1L1/PDGRFA fusion tyrosine kinase, which can be found in multiple cell lineages, including mast cells and eosinophils. This genetic abnormality is associated with increased mast cells in the bone marrow, an increased tryptase level, and peripheral eosinophilia, thus highlighting a role for non-KIT-dependent pathways in the pathogenesis of mast cell proliferation.<sup>12</sup>

### ***Pathologic Effects of Mast Cell Mediators***

After activation and degranulation, mast cells secrete and generate a host of mediators that contribute to allergic inflammation. The disease manifestations shown in mastocytosis are a consequence of increased mast cells present in tissue and the degree of release of mast cell mediators. **Table 1** summarizes the clinical features associated with mast cell mediators. Mast cell mediator release causes both local tissue and distal inflammation as they are released in to the bloodstream. Clinically, the most significant mediator is histamine. Histamine acts through 4 different receptors,  $H_1$  to  $H_4$ , to mediate vasopermeability, vasodilation, GI and bronchial smooth muscle contraction, gastric acid production and pruritus.<sup>13</sup>  $H_1$  receptors modulate bronchial and GI smooth muscle contraction and may be blocked by antihistamines such as diphenhydramine (Benadryl) and cetirizine (Zyrtec). Stimulation of gastric acid secretion by parietal cells is regulated by  $H_2$  receptors and is inhibited by  $H_2$  antagonists like ranitidine (Zantac). Mast cells have abundant secretory granule proteases, which make up most of the proteins present in mast cells, and the major protease is tryptase. Total tryptase comprises mature tryptase stored in granules and released only on activation and immature (pro) tryptase, which is constitutively secreted by the mast cell. Patients with mastocytosis generally have increased serum tryptase and histamine levels.<sup>14,15</sup> Other clinically relevant mediators are prostaglandin  $D_2$  and leukotriene  $C_4$ , which cause similar effects. Growth factor and inflammatory cytokines also produced by mast cells include interleukin 3 (IL-3), IL-16, and tumor necrosis factor  $\alpha$ .<sup>16</sup>

**Table 1**  
**Clinical manifestations and related mast cell mediators**

|                                  |                                                                                                        |
|----------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Skin</b>                      |                                                                                                        |
| Pruritus                         | Histamine, PAF                                                                                         |
| Flushing                         | PGD <sub>2</sub>                                                                                       |
| Urticaria                        | Histamine, PAF, LTC <sub>4</sub>                                                                       |
| Blistering                       | IL-6, tryptase, PGD <sub>2</sub> , PAF                                                                 |
| <b>Constitutional</b>            |                                                                                                        |
| Fatigue, weight loss, cachexia   | Tumor necrosis factor $\alpha$ , IL-1 $\beta$ , IL-6                                                   |
| <b>Systemic</b>                  |                                                                                                        |
| Hypotension and swelling         | Histamine, PAF, PGD <sub>2</sub> , LTC <sub>4</sub> , LTD <sub>4</sub> , LTE <sub>4</sub> , endothelin |
| Eosinophilia                     | IL-5                                                                                                   |
| Mast cell proliferation          | SCF, IL-3, IL-6, chymase                                                                               |
| Fibrosis                         | Transforming growth factor $\beta$                                                                     |
| Inhibition of localized clotting | Heparin                                                                                                |
| Lymphadenopathy                  | IL-16, lymphotaxin                                                                                     |
| <b>Gastrointestinal</b>          |                                                                                                        |
| Increased gastric acid           | Histamine                                                                                              |
| Intestinal cramping              | Histamine, PAF, LTC <sub>4</sub>                                                                       |
| <b>Skeletal system</b>           |                                                                                                        |
| Osteoporosis                     | Heparin, tryptase                                                                                      |
| <b>Lungs</b>                     |                                                                                                        |
| Bronchoconstriction              | Histamine, PGD <sub>2</sub> , PAF, LTC <sub>4</sub> , LTD <sub>4</sub> , endothelin                    |
| Mucus and edema                  | Histamine, PGD <sub>2</sub> , PAF, LTC <sub>4</sub> , proteases                                        |

*Abbreviations:* IL, interleukin; LT, leukotriene; PAF, platelet-activating factor; PG, prostaglandin; SCF, stem cell factor.

## CLINICAL FEATURES

### *Cutaneous Patterns of Mastocytosis*

All variants of mastocytosis share clinical features, but skin is the most common organ site of involvement and is often the first sign of the disease. In children, the skin may be the only manifestation of the disease.<sup>17</sup> In 2007, a proposed additional diagnostic category to the WHO nomenclature, termed mastocytosis of the skin (MIS), was introduced.<sup>18</sup> MIS proposes to assess disease status based on cutaneous findings, before performing a bone marrow biopsy. The diagnosis of MIS is based on the findings of a typical mastocytosis exanthema, comprising the major criterion, and 1 of 2 minor criteria as determined from a lesional skin biopsy showing either abnormal mast cells in clusters (>15) or more than 20 scattered per high-power field or detection of a dermal KIT mutation at codon 816. In terms of standard nomenclature, the term CM is reserved for cutaneous disease only and subdivided into maculopapular CM or urticaria pigmentosa (UP), DCM, mastocytoma, and telangiectasia macularis eruptiva perstans (TMEP).

The most common skin manifestation in both adults (**Fig. 2**) and children (**Fig. 3**) is UP, but the size and number are more variable in children with CM and they are more uniform in adults.<sup>19</sup> The typical appearance of UP are yellow-tan to reddish-brown macules or slightly raised papules scattered mainly on the trunk and legs, with generally less involvement of the sun-exposed areas. The palms, soles, face, and scalp are generally spared, especially in adults. Dermatologic symptoms include pruritus, flushing, and

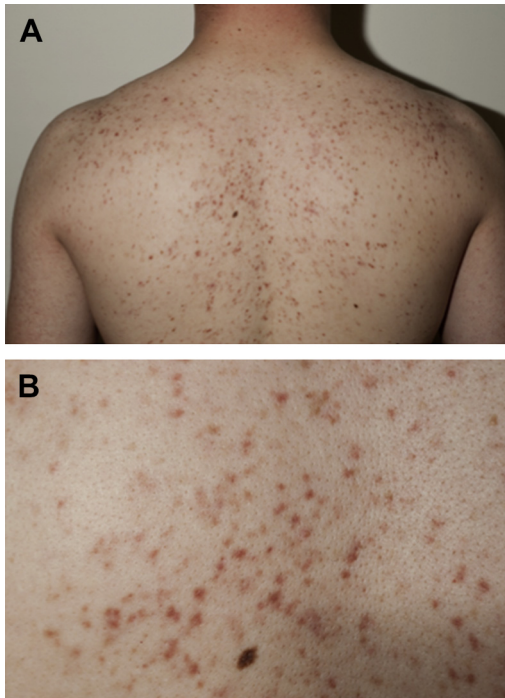


**Fig. 2.** Urticaria pigmentosa in an adult. (A) Typical maculopapular lesions of uniform size, generally less than 0.5 mm and (B) a closeup with color variation from red to brown.

blistering, with blistering almost uniquely seen in children. Darier sign is the local whealing of a lesion induced by friction but is inconsistently elicited. UP lesions are seen in greater than 90% of patients with ISM and less than 50% in patients with SM-AHNMD or ASM and may fade over time. Regression of the lesions may not indicate disease improvement. Studies in adults have reported lesional regression to be occasionally associated with increased serum tryptase levels and worsening disease.<sup>19-21</sup>



**Fig. 3.** Urticaria pigmentosa in a child. Tan papules and thin plaques on this child's back reflect the larger size of lesions that may be seen in children compared with those in adults. Lesions on sun-exposed areas such as the extremities tend to appear less active, as in this case.

DCM and mastocytomas have an onset almost exclusively in children. Although DCM may persist into adulthood, mastocytomas usually regress spontaneously. DCM is characterized by thickened skin and may show a peau d'orange appearance, with a reddish-brown discoloration without characteristic lesions of UP (Fig. 4A), but may also have scattered nodules similar in appearance to mastocytomas. The skin may be dermatographic, and the formation of hemorrhagic blisters is common. Bullous formation is limited to pediatric-onset cutaneous disease and is usually associated with lesional skin. Bullae may erupt spontaneously or in association with physical stimuli, infection, and immunization (see Fig. 4B). This feature is mostly limited to the first few years of life and may need to be distinguished from other bullous diseases of childhood. Solitary mastocytomas are red-brown or yellow-orange nodules, which when traumatized may cause systemic symptoms, such as flushing and hypotension (Fig. 5). Solitary mastocytomas generally appear before age 6 months, and it is unusual to develop subsequent skin lesions more than 2 months after the presentation of the initial lesion.<sup>17</sup> UP and DCM are associated with pruritus of varied intensity, which may be exacerbated by changes in climatic temperature, skin friction, and ingestion of hot beverages, spicy foods, alcohol, or certain drugs.

TMEP is the least common CM variant and is almost exclusively seen in adults. It appears as red-brown telangiectatic macules with irregular borders.

### GI Symptoms

GI symptoms in patients with mastocytosis are highly prevalent, often severe, and associated with decreased quality of life.<sup>22–25</sup> In a recent study of 83 patients with mastocytosis, the most common symptoms were diarrhea and bloating, followed by nausea and abdominal pain, all of which were significantly more frequent than in healthy age-matched individuals.<sup>23</sup> This recent study is consistent with an earlier report that abdominal pain and diarrhea are present in 80% of patients.<sup>22</sup> However, vomiting was less common and noted in less than 10% of patients. The risk of gastroduodenal ulcers was also found to be greater in these patients and was likely caused by increased gastric acid secretion that resulted from higher histamine production, consistent with other reports.<sup>22,23</sup> The frequency of GI symptoms did not seem to correlate with the presence of the D816V mutation or the level of serum tryptase nor the age of onset of mastocytosis.<sup>23,26</sup> Also, no correlation was found between histologic findings of mast cell infiltration in GI biopsies and GI symptoms. These symptoms

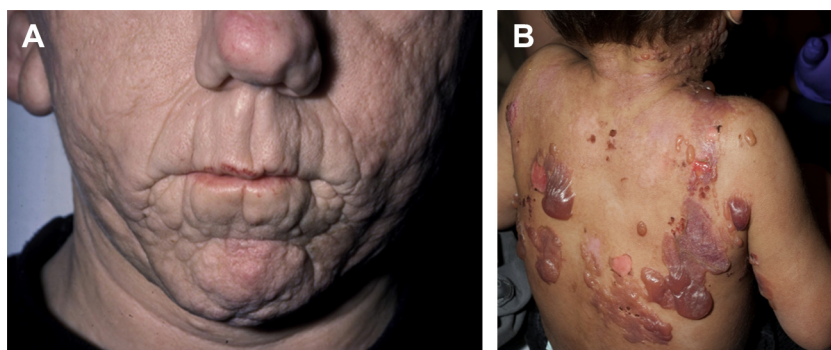


**Fig. 4.** DCM. (A) Diffuse dermal thickening, pachydermic flesh-colored lesions, and (B) bullous eruption in a child.



**Fig. 5.** Solitary mastocytoma on the foot sole of a child. A flat red-to-tan nodule with clearly defined border.

were similar to those in patients with inflammatory bowel disease. In an earlier prospective study,<sup>22</sup> most abdominal pain was dyspeptic, because it responded to H<sub>2</sub> antagonists, and most of these patients had increased gastric acid secretion. In addition to peptic ulcer disease, abdominal pain has been associated with edema of the GI tract, or motility dysfunction.<sup>27,28</sup>

In 1 study,<sup>22</sup> increased bowel movements and fecal output were reported in half of the patients, and in the patients in whom diarrhea was greater than 200 g stool/d, there was increased gastric acid secretion. Plasma histamine levels were also increased and correlated with basal acid output but not directly with abdominal pain or diarrhea. Gastric emptying and transit time did not differ between patients and control subjects with diarrhea and abdominal symptoms, and thus, transit time does not seem to be a major factor in GI symptoms.

Based on small studies and case reports, several GI peptides have been implicated in the pathogenesis of diarrhea and abdominal pain in patients with mastocytosis and include vasoactive intestinal peptide, neurotensin, substance P or motilin, and gastrin.<sup>22,29</sup> Although local secretion may play a role in GI signs and symptoms, it does not seem that systemic levels of these peptides are of major pathologic significance.

### ***Musculoskeletal Involvement***

Patients with systemic mastocytosis may have associated osteopenia or osteoporosis. Several patients with SM show roentgenographic findings of diffuse osteolysis and osteosclerosis, primarily affecting the axial skeleton and ends of the long bone.<sup>30</sup> Pathologic fractures or osteoporosis may be the presenting manifestation of mastocytosis. Musculoskeletal pain is a common presenting symptom. In a case series of 362 patients with mastocytosis,<sup>31</sup> 54% reported such pain and 18% felt it caused intolerable disability.

### ***Bone Marrow Pathology***

Systemic mastocytosis is usually diagnosed by bone marrow histopathology outlined by a WHO consensus panel (Box 2).<sup>11</sup> ISM, the most common variant of systemic disease, is diagnosed when criteria for mastocytosis are met and there is no evidence of an associated clonal hematologic disorder or severe liver disease, hypersplenism, or significant lymphadenopathy. Isolated bone marrow mastocytosis is a subvariant of ISM with a low bone marrow burden of mast cells, a lower tryptase value, and the absence of skin lesions. Several clinical conditions should heighten suspicion of this variant, such as idiopathic anaphylaxis, venom anaphylaxis, unexplained osteoporosis, or chronic diarrhea.<sup>32–35</sup>

**Box 2****Diagnostic criteria for cutaneous and systemic mastocytosis****CM**

Clinical findings consistent with urticaria pigmentosa, maculopapular CM, DCM, or solitary mastocytoma and typical mast cell infiltrates in a multifocal or diffuse pattern on skin biopsy

**Systemic Mastocytosis (SM)**

Major and 1 minor, or 3 minor, criteria are required for the diagnosis of SM

**Major Criteria**

- Multifocal dense infiltrates of mast cells ( $\geq 15$  mast cell in an aggregate) detected in bone marrow or other extracutaneous organs, and confirmed by tryptase immunohistochemistry (or other special stains)

**Minor Criteria**

- In biopsy sections of bone marrow or other extracutaneous organs, more than 25% of the mast cells in the infiltrates are spindle-shaped or have atypical morphology; or, of all mast cells in the bone marrow aspirate smears, more than 25% are immature or atypical mast cells
- Detection of Kit point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs
- Mast cells in bone marrow, blood, or other extracutaneous organs that coexpress CD117 with CD2 or CD25
- Baseline serum tryptase persistently greater than 20 ng/mL (if there is an associated clonal myeloid disorder, this parameter is invalid)

***Hepatic and Splenic Findings***

The liver, spleen, and lymph nodes are common organs affected in systemic mastocytosis, especially in patients with aggressive diseases. Specifically, the paratrabecular compartment of the spleen and paracortex of lymph nodes are more common sites of mast cell infiltration.<sup>36</sup> Other compartments may also be involved, with morphologic findings that pose challenges to identifying the source of the infiltration and may resemble other disease entities such as follicular and T-cell lymphoma, B-cell hyperplasia and lymphoma, Langerhans cell granulomatosis, and Kaposi sarcoma. Liver involvement is also common, but extreme liver disease is present only in those with aggressive disease. In a study of 41 patients with mastocytosis, 61% had indications of liver disease. Twenty-four percent had hepatomegaly, with most having increased liver enzyme levels. Increase in alkaline phosphatase levels correlated with hepatosplenomegaly, liver fibrosis, and increase in  $\gamma$ -glutamyl transpeptidase.<sup>37</sup> Other liver findings in patients with severe disease may include portal hypertension and ascites, but cirrhosis is not generally observed.

***Diagnosis***

Mastocytosis is diagnosed by history, clinical manifestations, histopathology, and laboratory evaluation. It is then classified as a variant based on WHO criteria (see **Boxes 1** and **2**).<sup>11</sup> The presenting constellation of mast cell mediator symptoms mentioned in the previous sections may be observed in patients with any variant of mastocytosis, both in adults and children.

The diagnosis of CM based on macroscopic appearance is confirmed with a lesional skin biopsy, showing characteristic skin histopathology (**Fig. 6**). Blind skin

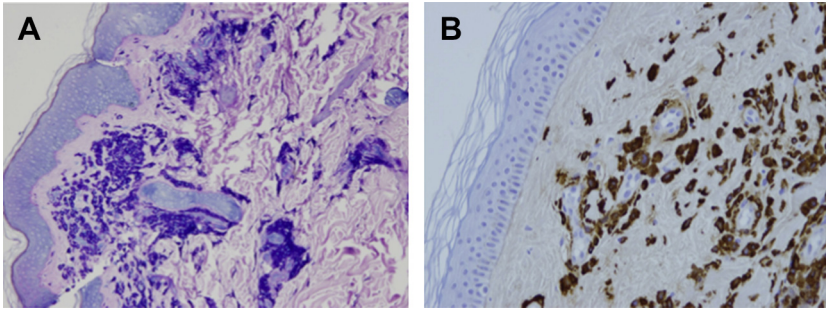


**Fig. 6.** Histopathology of urticaria pigmentosa from a 7-year-old. Clustering of normal and spindle-shaped mast cells in papillary dermis and extending into the reticular dermis. The tryptase stain highlights perivascular cuffing and interstitial presence of the mast cells. (A) Giemsa stain  $\times 40$ . (B) Tryptase stain  $\times 100$ .

biopsies are not recommended because other skin conditions, including eczema, may be associated with a 2-fold to 4-fold increase in dermal mast cells.<sup>38</sup> In addition, mast cells may also be increased in the skin in conditions such as scleroderma<sup>39</sup> and chronic urticaria,<sup>40</sup> and at sites of prolonged antigenic contact.<sup>41</sup> CM must also be distinguished from other diseases with similar characteristics, as presented in **Box 3**. UP lesions have mast cells in increased numbers in the dermal papillae beneath macules and papules, particularly near blood vessels in the upper dermis.<sup>38</sup> A bandlike infiltrate of mast cells may be seen in the papillary dermis. Mast cells also may appear as nodular infiltrates within the papillary dermis and subcutaneous tissues. Typically, there is a 15-fold to 20-fold increase in mast cells beneath UP lesions. Mast cells may also be found in increased numbers in the normal-appearing skin between lesions of UP.<sup>38</sup> The differences in the histologic pattern in cutaneous disease are generally based on the density of the mast cell infiltrate. In patients with DCM, mast cells are observed around blood vessels and throughout the dermis. These bandlike infiltrates may be indistinguishable from some lesions of UP or from biopsies obtained from mastocytomas. Cutaneous mast cell hyperplasia in patients with TMEP is present around the capillary venules of the superficial plexus. The biopsy of these lesions shows increased numbers of perivascular mast cells.

The diagnosis of mastocytosis should also be considered when a patient, primarily in the adult population, presents with 1 or more of the following: unexplained ulcer disease or malabsorption, radiographic or technetium-99 bone scan abnormalities, hepatomegaly, splenomegaly, lymphadenopathy, peripheral blood abnormalities, venom anaphylaxis, or unexplained flushing or hypotension.<sup>19,42–44</sup> In such patients, the diagnosis of systemic mastocytosis should be considered even in the absence of classic skin lesions.

The current approach to the workup of a patient for systemic mastocytosis consists of a medical evaluation, including a bone marrow biopsy and aspirate, a serum tryptase level, and an analysis for an activating mutation in KIT, preferably on bone marrow mononuclear cells. The diagnosis of systemic disease requires fulfilling the major criterion, consisting of multifocal dense mast cell aggregates, and 1 minor criterion; or 3 minor criteria (see **Box 2**). A bone marrow biopsy in those with pediatric-onset disease is not recommended unless there is evidence of systemic disease, as shown by hepatosplenomegaly, lymphadenopathy or unexplained peripheral blood abnormalities. The most useful stain for mast cells uses a monoclonal antibody to tryptase. In

**Box 3****Differential diagnosis of cutaneous mast cell manifestations**

## No apparent lesions

- Idiopathic flushing
- Anaphylaxis with identifiable cause
- Idiopathic anaphylaxis

## Diffuse or localized hyperpigmented macules or papules

- Café au lait spots
- Neurofibromatosis
- Albright syndrome
- Postinflammatory hyperpigmentation
- Secondary syphilis
- Chronic urticaria
- Atopic dermatitis
- Addison disease
- Lentigo

## Bullous eruptions

- Chronic bullous disease of childhood
- Linear IgA dermatosis
- Staphylococcus* infection
- Drug eruption
- Incontinentia pigmenti
- Bullous pemphigoid
- Bullous impetigo of infancy

## Solitary or multiple nodules

- Congenital nevus
- Juvenile xanthogranuloma
- Leukemia
- Lymphoma
- Neuroblastoma

addition, immunohistochemistry to identify CD25+ mast cells is of value, because CD25 has been shown to be expressed on most clonal mast cells in mastocytosis.<sup>45</sup>

Other tissue specimens, such as those from lymph nodes, spleen, liver, and GI mucosa, may help determine the extent of mast cell involvement, but are not typically necessary. GI biopsies are thus usually obtained only if a GI workup is indicated, and lymph nodes are biopsied only if lymphoma is considered. When biopsies have been obtained of involved tissue, the histopathologic pattern of mast cell aggregates is similar to that seen in the bone marrow and infiltrates are often CD25+.<sup>22,23,46</sup>

In patients suspected of having mastocytosis, the diagnosis of a carcinoid tumor or pheochromocytoma should be ruled out. Patients with mastocytosis do not excrete increased amounts of 5-hydroxyindoleacetic acid in the urine. Patients with carcinoid

tumor or pheochromocytoma also do not have histologic evidence of significant mast cell proliferation and should have normal serum tryptase levels.<sup>47</sup>

## TREATMENT

### *Mast Cell-Mediated Therapies*

The approach to treatment of patients with mastocytosis begins with management of mast cell-mediated symptoms such as pruritus, flushing, and GI cramping.<sup>48</sup> Specific triggers that cause mast cell mediator release should be avoided. These triggers may include physical and environmental stimuli, emotional stress, infections, medications, vaccinations, and anesthesia. Pruritus and flushing are often treated with an H<sub>1</sub> receptor antagonist such as hydroxyzine or nonsedating antihistamines such as cetirizine or fexofenadine. For additional relief, an H<sub>2</sub> antihistamine may be added such as ranitidine or famotidine. Some patients also benefit from the addition of a leukotriene inhibitor or disodium cromoglycate (cromolyn sodium), which may provide relief for GI symptoms.<sup>49</sup> Despite these medications, patients often continue to report headaches, flushing, GI symptoms, and musculoskeletal pain. This situation is likely caused by the inability of these agents to completely block histamine and other mast cell mediators.

Prompt administration of epinephrine is indicated for treatment of hypotensive episodes, which may be spontaneous or observed after insect stings and injection of contrast media.<sup>50</sup> Patients should be trained in self-administration of injectable epinephrine. Patients with recurrent episodes of hypotension may also benefit from prophylactic administration of H<sub>1</sub> and H<sub>2</sub> antihistamines. Psoralen taken orally in combination with ultraviolet light type A (PUVA) has been used to treat CM and relieve pruritus and flushing in adults.<sup>51,52</sup> In responsive patients, therapeutic effects are usually reached within 2 months, diminish with reduction in therapy, and return to baseline after discontinuation of therapy. Cutaneous mast cell lesions may also be effectively treated with topical corticosteroids under occlusive dressing, which leads to a reduction in the number of dermal mast cells at the treatment site.<sup>53,54</sup> Effects are transient.

### *GI Manifestations*

GI disease is treated with agents that inhibit gastric acid hypersecretion. In general, H<sub>2</sub> antagonists such as ranitidine and proton pump inhibitors like omeprazole are effective. Cromolyn sodium may reduce GI cramping.<sup>14</sup> Severe hepatosplenomegaly and ascites may respond to systemic corticosteroids.<sup>55</sup>

### *Osteoporosis and Fractures*

Patients with systemic disease may suffer from osteoporosis, and in some cases, a presenting feature may be a spontaneous bone fracture. A DEXA scan is used to evaluate bony involvement, including osteoporosis.<sup>56</sup> Treatment options are standard for mild osteoporosis and include calcium supplementation, bisphosphonate therapy, and estrogen replacement in postmenopausal woman. For aggressive disease, consider interferon  $\alpha$ -2b and 2-chlorodeoxyadenosine (cladribine/2-CdA), a nucleoside analogue.<sup>57</sup> Potential toxicities of 2-CdA are noteworthy and include myelosuppression and immunosuppression.<sup>58</sup>

### *Hematologic Involvement*

Patients with aggressive forms of systemic mastocytosis may be treated with interferon  $\alpha$ -2b,<sup>59</sup> and then 2-CdA. With regard to interferon  $\alpha$ -2b, several studies have shown varied responses, with some patients experiencing resolution of symptoms and others a partial or no response.<sup>60</sup> In addition, the side effects, which include fever, nausea, malaise, and a risk for anaphylaxis, should be considered before the initiation

of interferon  $\alpha$ -2b. In a study of 10 patients with severe systemic disease, 2CdA was shown to decrease symptoms and levels of mast cell mediators in most of the patients.<sup>61</sup>

For targeted therapies, it is important to determine if the D816V mutation is present. Imatinib (Gleevec), a tyrosine kinase inhibitor, has been shown to have a cytotoxic effect in vitro on mast cells that are wild type for KIT, but this effect is less in cells bearing the D816V mutation in KIT. This finding is consistent with the beneficial therapeutic effect of imatinib primarily on patients who do not carry the D816V mutation.<sup>62–64</sup>

Imatinib has been shown to be effective in a group of patients who present with increased mast cells in the bone marrow, increased tryptase levels and peripheral eosinophilia and have the FIP1L1/PDGRFA fusion mutation.<sup>65</sup> Other tyrosine kinase inhibitors, including PKC412 (midostaurin) and masitinib, are being evaluated for efficacy in clinical studies.<sup>66–68</sup> Hematopoietic stem cell transplant was performed in 3 patients, and all encountered disease progression.<sup>69</sup> In patients with severe mast cell disease, splenectomy may improve survival.<sup>70</sup>

### Prognosis

In general, children have a more favorable prognosis.<sup>17,21,71,72</sup> Children with CM often experience total or major disease regression by late adolescence.<sup>18,21,73</sup> The resolution of cutaneous disease in adults may correlate with the reduction in clinical skin symptoms but may not indicate disease regression. With adults experiencing a significant reduction in skin lesions, the bone marrow typically continues to show mast cell involvement and a diagnosis of systemic disease by WHO criteria is maintained or confirmed.<sup>18,20</sup> The life expectancy in adult patients with CM and ISM parallels that of the general population.

Patients with SM-AHNMD have a disease course determined by the response of the associated hematologic disorder to therapy. Although there are some cases reports of SM-AHNMD in children,<sup>74–77</sup> this variant is more often seen in adults. ASM and MCL are rare variants, with less favorable outcomes. ASM has a better survival with aggressive cytoreductive therapy, but no therapeutic intervention has reliably extended the life expectancy of patients with MCL.

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