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Mastocytosis

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Article Synopsis

Mastocytosis is a disorder of abnormal mast cell proliferation with clinical features that include flushing, pruritus, abdominal pain, diarrhea, hypotension, syncope and musculoskeletal pain. These features are the result of mast cell mediator release and infiltration into target organs. Patients of all ages may be affected, although in children manifestations primarily involve the skin. Most patients with systemic disease have a somatically acquired activating mutation in the KIT oncogene. This article encapsulates the etiology and pathogenesis of mastocytosis with an overview of the clinical features and the approach to diagnosis, evaluation and therapy in adults and pediatric patients.

Keywords

Mast cell; mastocytosis; KIT; bone marrow; skin; urticaria

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 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, mastocytoma, and telangiectasia macularis eruptiva perstans. Mastocytosis occurs in both children and adults, although children tend to primarily manifest cutaneous lesions. Most cases appear to be spontaneous. Inherited patterns of mastocytosis are unusual.

Mastocytosis has been classified into disease variants, which are listed in Box 1 according to a WHO consensus.¹ 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. 6) 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

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non-mast-cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL) and mast cell sarcoma (MCS). Of these MCL, although rare, is the most aggressive and may be characterized by the presence of immature mast cells in peripheral blood.

Box 1

WHO Classification of Mastocytosis

Cutaneous mastocytosis (CM)

Urticaria pigmentosa (UP) = maculopapular CM (MPCM)

Diffuse cutaneous mastocytosis (DCM)

Mastocytoma of skin

Indolent systemic mastocytosis (ISM)

Smoldering SM

Isolated bone marrow mastocytosis

Systemic mastocytosis with associated clonal, hematologic non-mast-cell lineage disease (SM-AHNMD)

Aggressive systemic mastocytosis (ASM)

Mast cell leukemia (MCL)

Mast cell sarcoma (MCS)

Extracutaneous mastocytoma

WHO, World Health Organization.

Etiology and Pathogenesis

Mast cell origin, growth and development

Human mast cells develop from CD34⁺ pluripotent progenitor cells.²⁻⁵ 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 in proximity to blood vessels, nerves and glandular structures. They are particularly numerous in the skin, gastrointestinal 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.⁶ 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.⁷ Activating somatic mutations in *c-kit* that 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, Asp816Val (D816V), is located in catalytic domain of KIT and results in augmented mast cell proliferation and survival.^{8, 9} The D816V mutation is less common in children, especially in those with cutaneous mastocytosis. Other *c-kit* mutations including V560G, D816Y, D816F, D816H and E839K have been identified in mast cell lines, mast cell leukemia and pediatric mastocytosis.^{10, 11} Whether these are activating mutations or contribute to ligand independent activation and suppression of apoptosis has not been fully elucidated. A subgroup of patients that 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 elevated tryptase

and peripheral eosinophilia, thus highlighting a role for non-KIT dependent pathways in the pathogenesis of mastocytosis.¹²

Pathologic effects of mast cell mediators

Following activation and degranulation, mast cells secrete and generate a host of mediators that contribute to allergic inflammation. The disease manifestations exhibited 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 four different receptors, H₁–H₄, to mediate vasopermeability, vasodilation, gastrointestinal and bronchial smooth muscle contraction, gastric acid production and pruritus.¹³ H₁ 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 H₂ receptors and is inhibited by H₂ 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 is comprised of mature tryptase stored in granules and released only upon activation and immature (pro) tryptase, which is constitutively secreted by the mast cell. Patients with mastocytosis generally have elevated serum tryptase and histamine.^{14, 15} Other clinically relevant mediators are prostaglandin D₂ and leukotriene C₄, which cause similar effects in human lung mast cells. Growth factor and inflammatory cytokines also produced by mast cells include interleukin-3 (IL-3), IL-16 and tissue necrosis factor- α (TNF- α).¹⁶

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.¹⁷ In 2007, a proposed additional diagnostic category to the WHO nomenclature, termed “mastocytosis of the skin” (MIS), was introduced.¹⁸ MIS proposes to assess disease status based on cutaneous findings, prior to performing a bone marrow biopsy. The diagnosis of MIS is based on the findings of a typical mastocytosis exanthema, comprising the major criterion, and one of 2 minor criteria as determined from a lesional skin biopsy showing either abnormal mast cells in clusters (>15) or >20 scattered per HPF and/or detection of a dermal KIT mutation at codon 816. In terms of standard nomenclature, the term cutaneous mastocytosis (CM) is reserved for cutaneous disease only and subdivided into maculopapular CM (MPCM) or urticaria pigmentosa (UP), diffuse cutaneous mastocytosis (DCM), mastocytoma, and telangiectasia macularis eruptiva perstans (TMEP).

The most common skin manifestation in both adults (Fig. 1) and children (Fig. 2) is UP, but the size and number are more variable in children with CM and more uniform in adults.¹⁹ 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 included pruritus, flushing, and blistering with the latter symptom almost uniquely seen in children. Darier’s sign is the local whealing of a lesion induced by friction but is inconsistently elicited. UP lesions are seen in greater than 90 percent of patients with ISM, less than 50 percent in patients with SM-AHNMD or ASM and may fade over time. Regression of the lesions may not be indicative of disease improvement. Studies

in adults have reported lesional regression to be occasionally associated with elevated serum tryptase and worsening disease.^{19–21}

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 exhibit a peau d'orange appearance with a reddish-brown discoloration without characteristic lesions of UP (Fig. 3a), 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 usually is associated with lesional skin. Bullae may erupt spontaneously or in association with physical stimuli, infection and immunization (Fig 3b). 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. 4). Solitary mastocytomas generally appear before age 6 months and it is unusual to develop subsequent skin lesions more than two months after the presentation of the initial lesion¹⁷. 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.

Gastrointestinal symptoms

Gastrointestinal symptoms in patients with mastocytosis are highly prevalent, often severe and associated with decreased quality of life.^{22–25} 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 aged matched subjects.²³ This recent study is consistent with an earlier report that abdominal pain and diarrhea are present in 80% of patients.²² Vomiting, however, 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 likely due to increased gastric acid secretion that resulted from higher histamine production, consistent with other reports.^{22, 23} Interestingly, the frequency of gastrointestinal 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.^{23, 26} There was also no correlation found between histological findings of mast cell infiltration in gastrointestinal biopsies and gastrointestinal symptoms. These symptoms were similar to those in patients with inflammatory bowel disease. In an earlier prospective study most abdominal pain was dyspeptic as it responded to H₂ antagonists and the majority of these patients has increased gastric acid secretion.²² In addition to peptic ulcer disease, abdominal pain has been associated with edema of the GI tract, or motility dysfunction.^{27, 28}

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

Based on small studies and case reports, a number of gastrointestinal 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.^{22, 29} Although local secretion may play a role in GI symptomatology, it does not appear that systemic levels of these peptides are of major pathological significance.

Musculoskeletal involvement

Patients with systemic mastocytosis may have associated osteopenia or osteoporosis. A number of patients with SM exhibit roentgenographic findings of diffuse osteolysis and osteosclerosis, primarily affecting the axial skeleton and ends of the long bone.³⁰ 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, 54% reported such pain and 18% felt it caused intolerable disability.³¹

Bone marrow pathology

Systemic mastocytosis is usually diagnosed on the basis of bone marrow histopathology outlined by a WHO consensus panel (Box 2).¹¹ 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 sub-variant 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.^{32–35}

Box 2

Diagnostic Criteria for Cutaneous and Systemic Mastocytosis

Cutaneous Mastocytosis (CM)

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

Systemic Mastocytosis (SM)

Major and one Minor or Three minor criteria are required for the diagnosis of SM

Major Criteria

- Multifocal dense infiltrates of mast cells (≥ 15 mast cell in an aggregate) detected in in bone marrow and/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 co-express CD117 with CD2 and/or CD25.
- Baseline serum tryptase persistently > 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.³⁶ 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's 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 the majority having elevation in liver enzymes. Elevation in alkaline phosphatase levels correlated with hepatosplenomegaly, liver fibrosis and elevation in γ -glutamyl transpeptidase (GGTP).³⁷ Other liver findings in patients with severe disease may include portal hypertension and ascites but cirrhosis is not generally observed.

Diagnosis

Mastocytosis is diagnosed on the basis of history, clinical manifestations, histopathology and laboratory evaluation. It is then classified as to variant based on WHO criteria (Box 1 and Box 2).¹¹ 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 cutaneous mastocytosis based on macroscopic appearance is confirmed with a lesional skin biopsy demonstrating characteristic skin histopathology (Fig. 5). Blind skin biopsies are not recommended since other skin conditions, including eczema, may be associated with a two- to fourfold increase in dermal mast cells.³⁸ In addition, mast cells may also be increased in the skin in conditions such as scleroderma³⁹ and chronic urticaria⁴⁰; and at sites of prolonged antigenic contact⁴¹. Cutaneous mastocytosis 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.³⁸ A band-like 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- 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.⁴² 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 band-like 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 reveals increased numbers of perivascular mast cells.

Box 3

Differential diagnosis of Cutaneous Mast Cell Manifestations

No apparent lesions

- Idiopathic flushing
- Anaphylaxis with identifiable cause
- Idiopathic anaphylaxis

Diffuse or localized hyper-pigmented macules or papules

Café au lait spots
 Neurofibromatosis
 Albright syndrome
 Post-inflammatory hyperpigmentation
 Secondary syphilis
 Chronic urticaria
 Atopic dermatitis
 Addison's 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

The diagnosis of mastocytosis should also be considered when a patient, primarily in the adult population, presents with one or more of the following: unexplained ulcer disease or malabsorption, radiographic or ⁹⁹Tc bone scan abnormalities, hepatomegaly, splenomegaly, lymphadenopathy, peripheral blood abnormalities, venom anaphylaxis, or unexplained flushing or hypotension^{19, 43–45}. In such patients, the diagnosis of systemic mastocytosis should be considered even in the absence of classic skin lesions.

The current approach to the work-up 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 one minor criterion; or three minor criteria (Box 2). A bone marrow biopsy in those with pediatric-onset disease is not recommended unless there is evidence of systemic disease as demonstrated by hepatosplenomegaly, lymphadenopathy or unexplained peripheral blood abnormalities. The most useful stain for mast cells utilizes a monoclonal antibody to tryptase. In addition, immunohistochemistry to identify CD25+ mast cells is of value since CD25 has been shown to be expressed on most clonal mast cells in mastocytosis.⁴⁶

Other tissue specimens, such as those from lymph nodes, spleen, liver, and gastrointestinal mucosa, may help determine the extent of mast cell involvement, but are not typically necessary. Gastrointestinal biopsies are thus usually obtained only if a gastrointestinal 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+. ^{22, 23, 47}

In patients suspected of having mastocytosis, the diagnosis of a carcinoid tumor or pheochromocytoma should be ruled out. Importantly, patients with mastocytosis do not excrete increased amounts of 5-HIAA 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. ⁴⁸

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 gastrointestinal cramping. ⁴⁹ Specific triggers that cause mast cell mediator release should be avoided. These may include physical and environmental stimuli, emotional stress, infections, medications, vaccinations, and anesthesia. Pruritus and flushing are often treated with an H1 receptor antagonist such as hydroxyzine or non-sedating antihistamines such as cetirizine or fexofenadine. For additional relief, an H2 antihistamine may be added such as ranitidine or famotidine. Some patients will also benefit from the addition of a leukotriene inhibitor or disodium cromoglycate (cromolyn sodium), which may provide relief for gastrointestinal symptoms. ⁵⁰ Despite these medications, patients often continue to report headaches, flushing, gastrointestinal symptoms and musculoskeletal pain. This is likely due to 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 that may be spontaneous, or observed following insect stings and injection of contrast media. ⁵¹ Patients should be trained in self-administration of injectable epinephrine. Patients with recurrent episodes of hypotension may also benefit from prophylactic administration of H1 and H2 antihistamines. Psoralen taken orally in combination with ultraviolet light type A (PUVA) has been used to treat cutaneous mastocytosis and relieve pruritus and flushing. ^{52, 53} In responsive patients, therapeutic effects are usually reached within two months, diminish with reduction in therapy and return to baseline following 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. ^{54, 55} Effects are transient.

Gastrointestinal manifestations

GI disease is treated with agents that inhibit gastric acid hypersecretion. In general, H2 antagonists such as ranitidine and proton pump inhibitors like omeprazole are effective. Cromolyn sodium may reduce gastrointestinal cramping. ¹⁴ Severe hepatosplenomegaly and ascites may respond to systemic corticosteroids. ⁵⁶

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. ⁵⁷ Treatment options are standard for mild osteoporosis

and include calcium supplementation, bisphosphonate therapy, and estrogen replacement in postmenopausal woman. For aggressive disease, consider interferon- α -2b and 2-chlorodeoxyadenosine (cladribine/2-CdA.), a nucleoside analogue.⁵⁸ Potential toxicities of 2-CdA are noteworthy and include myelosuppression and immunosuppression.⁵⁹

Hematologic involvement

Patients with aggressive forms of systemic mastocytosis may be treated with interferon- α -2b,⁶⁰ and then 2-CdA. With regard to interferon α -2b, several studies have shown varied responses, with some patients experiencing resolution of symptoms, others a partial or no response.⁶¹ In addition, the side effects, which include fever, nausea, malaise and a risk for anaphylaxis, should be considered before the initiation of interferon α -2b. In a study of 10 patients with severe systemic disease, 2CdA was shown to decrease symptoms and levels of mast cell mediators in the majority of the patients.⁶²

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.^{63–65}

Imatinib has been shown to be effective in a group of patients that present with increased mast cells in the bone marrow, elevated tryptase and peripheral eosinophilia and have the FIP1L1/PDGRFA fusion mutation.⁶⁶ Other tyrosine kinase inhibitors including PKC412 (midostaurin) and masitinib and are being evaluated for efficacy in clinical studies.^{67–69} Hematopoietic stem cell transplant was performed in three patients but all eventually encountered disease progression.⁷⁰ In patients with severe mast cell disease splenectomy may improve survival.⁷¹

Prognosis

In general, children have a more favorable prognosis.^{21, 72–74} Children with cutaneous mastocytosis often experience total or major disease regression by late adolescence.^{18, 21, 75} 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 demonstrate mast cell involvement and a diagnosis of systemic disease by WHO criteria is maintained or confirmed.^{18, 20} The life expectancy in adult patients with cutaneous mastocytosis 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 SMAHNMD in children,^{76–79} 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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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 non-aggressive variants of mastocytosis.
- Patients with aggressive disease may benefit from cytoreductive therapies.

Figure 1. Urticaria Pigmentosa in an adult

A) Typical maculo-papular lesions of uniform size, generally $<0.5\text{mm}$ and B) a close up with color variation from red to brown.

Figure 2. Urticaria pigmentosa in a child

Tan papules and thin plaques on this child's back reflect the larger size of lesions, which may be seen in children in comparison to those in adults. Lesions on sun-exposed areas such as the extremities tend to appear less active as in this case.

Figure 3. Diffuse cutaneous mastocytosis

A) Diffuse dermal thickening, pachydermic flesh colored lesions and B) Bullous eruption in a child.

Figure 4. Solitary mastocytoma on the foot sole of a child
A flat red to tan nodule with clearly defined border.

Figure 5. Histopathology of Urticaria Pigmentosa from a 7 yr 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 40X B) Tryptase stain 100X.

Figure 6. Bone marrow histopathology in an adult with Indolent Systemic Mastocytosis Mast cell aggregates demonstrated by staining with tryptase in A) (40X); and B) highlights the mast cell component of the aggregate and the prominent abnormal spindle-shaped mast cells (100X).

Table 1

Clinical manifestations and related mast cell mediators

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

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