

# Mastocytosis: Mediator-Related Signs and Symptoms

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## Key Words

Mastocytosis · Mediators · Symptoms-signs · Flushing

## Abstract

Patients with systemic mastocytosis present symptoms related to the tissue response to the release of mediators from mast cells and to the local mast cell burden. Such patients often have a history of chronic and acute mediator-related symptoms. Most patients have indolent disease with a good prognosis and a normal life span. Symptoms can include pruritus, flushing, syncope, gastric distress, nausea and vomiting, diarrhea, bone pain and neuropsychiatric symptoms, most of which are controlled by medication. Because there is no current cure for mastocytosis, successful therapeutic interventions rely on the recognition of mediator-related symptoms and their treatment, and established intervention approaches for the relatively uncommon leukemic concomitants. Efforts to link a particular mast cell-derived mediator to some aspect of the symptom complex depend on the known actions of the mediator and the efficacy of target-based interventions.

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Mastocytosis is a disease characterized by an abnormal increase in tissue mast cells. Current classification defines cutaneous mastocytosis (CM) as a mast cell hyperplasia limited to the skin and systemic mastocytosis (SM) as multiple distinct entities in which mast cells infiltrate the skin and/or other organs [1]. The diagnosis of SM is based on 1 major criterion [multifocal dense infiltrates of >15 MC in bone marrow (BM) and/or other extracutaneous organs] and 1 minor criterion or 3 minor criteria. Four minor criteria have been defined: serum tryptase levels >20 ng/ml, the expression of CD2 and CD25 surface markers in c-kit-positive mast cells from BM or other organs, the presence of a c-kit mutation and the presence of >25% abnormal spindle-shaped mast cells in BM and/or tissues [1].

Patients with CM and SM present symptoms related to the tissue response to the release of mediators from mast cells and to the local mast cell burden. CM is easily recognized by typical skin lesions, the most frequent being urticaria pigmentosa (UP). Patients with SM often have a history of chronic and acute mediator-related symptoms. Most patients with SM have indolent disease (ISM) with a good prognosis and a normal life span. Symptoms can include pruritus, flushing, syncope, gastric distress, nausea and vomiting, diarrhea, bone pain and neuropsychiatric symptoms, most of which are controlled by medication [2]. Poor prognosis is associated with aggressive forms

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(ASM), SM associated with a hematological non-mast cell clonal disorder (SM-AHNMD) and mast cell leukemia (MCL). The incidence of atopic diseases such as asthma and allergic rhinitis is the same as in the general population [3].

Any effort to link a particular mast cell-derived mediator to some aspect of the symptom complex of CM or SM depends on the known actions of the mediator and the efficacy of target-based interventions at best and is pure conjecture in most other contexts.

### **General and Constitutional Symptoms**

Constitutional symptoms including fatigue, weight loss, fever and sweats have been reported by patients with long-standing multiorgan ISM and can be the presenting symptoms for ASM and MCL [4]. Fatigue, usually mild, is the most frequent symptom. Fever and sweats are less frequent and generally absent in patients with ISM [2]. Anorexia can be associated with severe gastrointestinal symptoms but malnutrition or severe loss of weight are not observed. Cytokines such as TNF $\alpha$ , IL-1 $\beta$  and IL-6 could contribute to the constitutional symptoms, but evidence of their mast cell origin is limited to *in vitro* studies.

### **Cutaneous Signs and Symptoms**

The consequences of mast cell accumulation in the skin include the spontaneous or induced release of mast cell mediators leading to flushing, pruritus, urticaria and dermatographism. These symptoms can occur in patients with CM and SM. The rubbing of UP lesions and mastocytomas leads to urtication and flare described as the Darier's sign. Episodic flushing is present in patients with UP, mastocytomas, and in patients with diffuse CM [5]. Pruritus and dermatographism are associated with UP, mastocytomas and diffuse CM and can be exacerbated by alcohol or surface friction [2, 4]. In children the onset of mastocytosis is most frequently associated with skin symptoms of pruritus and flushing [6]. Blistering can occur in patients with UP, mastocytomas and in most cases of diffuse disease [5]. Prolonged skin bleeding is a rare and serious complication of bullous mastocytosis in children [7].

In UP and mastocytoma lesions, mast cells accumulate in the papillary dermis and around blood vessels and can extend into the subcutaneous tissues. In diffuse and erythrodermic forms, mast cells infiltrate the dermis in a

band-like fashion [5]. The morphology of the cutaneous mast cells is not uniform. UP lesions can present fibroblast-like, elongated mast cells with profuse granulation and multiple cytoplasmic interdigitating villi and mastocytomas can present round mast cells with fewer granules [8]. EM and immunochemistry studies indicate that UP mast cells have gratings and lattice and express tryptase, chymase and mast cell carboxypeptidase A (as distinct from pancreatic)-like normal skin mast cells [9]. Suspensions of mast cells from lesional UP skin biopsies release histamine in response to IgE cross-linking, C3a or calcium ionophore [10], like normal mast cells dispersed from tissues.

Regulation of mast cell homing is dictated by the expression of surface receptors including integrins [11] and the tissue concentration of receptor ligands, cytokines and chemokines. Preferential accumulation of mast cells in the skin indicates a tissue response to mast cell surface receptors. Increased interstitial stem cell factor (SCF) has been found in the lesions and normal skin of patients with UP with normal levels of mRNA, implying a posttranslational dysregulation [12]. Circulating and immature tissue mast cells in a patient with ASM expressed cell-bound SCF, suggesting a possible autocrine regulation of the mast cell hyperplasia in some circumstances [13]. Mutations of the c-kit receptor (as discussed in detail elsewhere in this volume) are present in UP mast cells in adults with SM and in a subset of children with CM [14]. Such mutations drive proliferation but appear to allow adhesion/migration to cell-associated and free SCF [15]. Effective inhibition of spontaneous flushing is achieved with high doses of aspirin in some patients with SM indicating that PGD<sub>2</sub> could be involved [16]. The combination of H<sub>1</sub> and H<sub>2</sub> antihistamines has been effective at relieving the pruritus and urticaria of patients with ISM and UP [2]. The administration of psoralen plus ultraviolet A (PUVA) photochemotherapy decreases pruritus, fades UP lesions in adults and decreases the formation of bullae in children with diffuse CM. The effect is attributed to a decrease in skin mast cell numbers, a finding supported by a decrease in urinary histamine [5].

### **Gastrointestinal Symptoms**

Gastrointestinal symptoms are the second most frequent complaints in patients with mastocytosis after pruritus and flushing. Because these symptoms are chronic and often severe, they are associated with significant morbidity unless treated. Adult patients with SM have fre-

quent gastrointestinal complaints, the most common being abdominal pain and diarrhea [2, 4, 17]. Nausea and vomiting are less frequent.

Patients present two types of upper abdominal pain: a typical dyspeptic pain and a nondyspeptic discomfort [2, 4]. Dyspeptic pain is associated with peptic disease and changes in the duodenum on endoscopic and radiological studies [17]. Nondyspeptic pain occurs often in association with alcohol, certain foods and stress [2, 4], and patients with nondyspeptic pain can present with prominent gastric and duodenal folds with nodular lesions [17]. Some of these lesions assessed in biopsies have an increased number of mast cells in the lamina propria and submucosa. A selective deficiency of IgA in the duodenal fluid has been described in association with SM [17].

Involvement of the small intestine beyond the duodenum can present as malabsorption or as crampy lower abdominal pain with diarrhea or rarely with both. Mild steatorrhea is present in some patients with SM [4]. Small intestine absorptive defects have been documented by the D-xylose absorption test [18]. Malabsorption of fat-soluble vitamins can rarely lead to tetany, osteomalacia and vitamin A deficiency with defects in night vision [17]. Radiographic studies show structural abnormalities with small bowel thickening, nodularity or polypoid lesions [19]. Histological changes include blunted villi and mucosal nodules with an increased number of mast cells in association with neutrophil and eosinophil infiltration [19]. Diarrhea is present in patients with SM and is described by some patients as multiple loose or semi-formed stools per day [2, 4]. Anorectal manometry shows decreased rectal compliance and increased contractility [20], and endoscopic and barium studies show small nodules and polypoid lesions in the colon [17].

Although histamine is a potent stimulant of gastric secretion and the majority of patients with SM have increased histamine levels in blood or urine or both, acid hypersecretion is not a consistent finding in SM patients with abdominal symptoms [17]. Some studies have documented gastric hypersecretion in the range of patients with Zollinger-Ellison and other studies have documented achlorhydria despite increased histamine levels. The parietal mast cell mass is normal in most of the patients with ISM, consistent with the notion that gastrin but not histamine induces gastric parietal cell hyperplasia [17]. Maximal acid output in response to pentagastrin is normal in most patients with ISM and there is no elevation of gastrin, VIP, motilin or substance P [18].

Antihistamine H<sub>1</sub> and H<sub>2</sub> blockers have been effective at reducing acid hypersecretion in patients with peptic

ulcer disease and in some patients at reducing or controlling diarrhea [2], implicating histamine as the mediator. Patients with severe diarrhea unresponsive to H<sub>1</sub> and H<sub>2</sub> blockade have been successfully treated with sodium cromolyn administered orally. It is minimally absorbed and its efficacy in controlling the abdominal pain and diarrhea is attributed to direct stabilization of the intestinal mast cell population. The apparent concomitant benefit in cognitive function is inexplicable [21]. Corticosteroids are used to alleviate malabsorption due to increased intestinal mast cell mass.

Increased liver size presents in long-standing ISM with no impairment of liver function and minimal elevation of liver enzymes [2]. Elevation of AP in patients with hepatomegaly has been associated with liver size, the extent of the fibrosis and the mast cell mass [22], but it could also reflect skeletal involvement in such patients. Portal hypertension is reported and attributed to intrahepatic venous obstruction due to portal and sinusoid fibrosis [4]. Transudative ascites can develop in patients with portal hypertension. Liver scans with a diffuse abnormal uptake pattern in ISM would be consistent with diffuse parenchymal disease. The most frequent finding on liver biopsy is an increase in portal fibrosis and prominent mast cell infiltrates in portal spaces and to a lesser extent in the sinusoids in association with eosinophilia [23]. Inflammatory changes with focal necrosis or cirrhosis are also reported [17]. Liver mast cells in patients with ISM exhibit typical phenotypic characteristics of skin mast cells.

### **BM and Lymphatic Tissues**

Patients with SM present mild to moderate increases of BM mast cells with the key diagnostic criteria being phenotype presentation, except in MCL where extensive infiltration of atypical mast cells is found with replacement of the normal marrow architecture [24]. SM-AHNMD presents typical BM abnormalities relating to the hematological malignancy. Patients with ASM and long-standing ISM can present extensive BM fibrosis with concomitant decrease in other lineages and extramedullary hematopoiesis [13].

Splenomegaly is frequent in patients with ASM, SM-AHNMD and MCL and patients with ISM may develop splenomegaly over time [2]. Histological data from 52 surgically removed spleens of patients with ASM, SM-AHNMD and MCL showed enlarged spleens with a thickened capsule due to fibrosis. The parenchyma presented nodular areas consistent with fibrosis and cellular infiltra-

tion similar to T cell lymphomas or granulomatous processes [25]. Extramedullary hematopoiesis is present in a variable degree. Mast cell infiltration is prominent with two different patterns: a diffuse infiltration involving the cords and the sinuses of the red pulp and a focal infiltration involving the white pulp around the follicles and periarteriolar spaces [25]. Eosinophils are frequently associated with mast cell infiltrates. In a patient with ASM, the spleen presented poorly metachromatic immature tryptase-positive mast cells expressing c-kit and SCF, in addition to mature metachromatic mast cells expressing tryptase, chymase and carboxypeptidase A (CPA) [13].

Central or peripheral lymphadenopathy occurs in aggressive forms such as ASM, AHNMD and MCL [26]. Lymph nodes can enlarge during long-standing ISM. Mast cell infiltration can be focal or diffuse with partial or total disruption of the normal architecture of the lymph node. Eosinophilia, fibrosis and extramedullary hematopoiesis are associated with mast cell infiltrates [26]. Mast cells in lymphadenopathies are highly metachromatic and express tryptase, chymase and CPA as in skin and spleen. Immature poorly metachromatic mast cells expressing c-kit and SCF were also found in a patient with ASM [13]. Dysgammaglobulinemia with increased levels of IgG and IgM and monoclonal IgG k on serum electrophoresis has been found in a small proportion of patients with ISM, suggesting that the mast cell may be providing IL-6 [2, 4].

Fibrotic changes in patients with SM are present in the BM, liver, spleen and lymphadenopathies implicating IL-13 and TGF $\beta$  as the mediators. Tissue eosinophilia may result from local mast cell release of IL-5.

### **Skeletal Symptoms**

Bone pain is present in SM and usually affects long bones [4]. Asymptomatic patients can present radiographic changes which include osteopenic, lytic or sclerotic changes often interpreted as osteoporosis, metastatic disease, Paget's disease of the bones or multiple myeloma [4]. Pelvic bones, skull, ribs, hands, spine and femur are frequently affected. Bone scans demonstrate multifocal abnormalities and in some cases diffuse increased uptake. Vertebral compression fractures are not common [2]. Bone remodeling could be attributed to the mast cell mass as well as IL-1 $\beta$  and IL-6 cytokines secreted by mast cells.

### **Cardiovascular Symptoms**

Spontaneous syncope and episodic vascular collapse are the most dramatic acute manifestation of SM [2, 4]. The severity and frequency of the episodes vary and fatalities have been described in patients with severe and prolonged hypotension. The episodes can be preceded by lightheadedness and can occur as frequently as daily or as rarely as once a year. Spontaneous resolution is usual and documentation of hypotension is infrequent. Some patients experience retrograde amnesia. Palpitations with tachycardia can precede lightheadedness induced by sudden systemic vasodilatation and hypotension [2, 4].

Chest pain has been described in patients with SM and normal coronary arteries by angiography but abnormal stress test [27]. No data is available on the frequency and phenotype of cardiac mast cells in SM patients. Mast cells are present in the normal heart and concentrate around blood vessels and coronary arteries. The morphology is similar to that of the skin mast cells as is also their response to secretagogues [27, 28]. In dogs, cardiac mast cells release histamine and TNF $\alpha$  during acute myocardial ischemia and have been implicated in the pathogenesis of myocardial injury [29]. Reduction in the severity of the episodes of syncope and acute vascular collapse has been shown with the use of aspirin with the concomitant reduction in urinary excretion of PGD<sub>2</sub> metabolites [30]. Thus, both PGD<sub>2</sub> and histamine are implicated in such events.

### **Neuropsychiatric Symptoms**

Headache is the most frequent complaint and has a heterogeneous presentation: a typical mild frontal, dull, nonpounding headache responsive to NSAIDs, a vascular headache with migraine characteristics responsive to class medications, and a headache associated with rhinorrhea, pruritus, lacrimation suggestive of a histaminergic variety. Chronic symptoms include decreased attention span, difficulty in concentration, forgetfulness, irritability or depression and are described as mixed organic brain syndrome [31]. Poor motivation, confusion, anger, anxiety, lethargy and sleepiness are also reported. Nonspecific EEG abnormalities have been noted in a proportion of patients with these complaints [2].

Mast cells are residents of the normal nervous system and localize in the infundibulum, pineal, area postrema, choroid plexus, thalamic areas, parietal cortex and connective tissue of the leptomeninges in a perivascular loca-

tion. The frequency and morphology of mast cells in the brain in SM patients have not been studied and measurements of mediators in the brain are lacking. PGD<sub>2</sub> has been implicated in sleep/awake patterns based on the findings in transgenic mice and rats [32, 33].

Cromolyn sodium given orally has been effective at improving the mixed organic brain syndrome [34], indicating that local intestinal mast cell stabilization could contribute to preventing the release of mediators affecting the CNS.

### Pulmonary Symptoms

Pulmonary symptoms are rare in patients with SM whereas nasal manifestations are more frequent [2, 4]. Rhinitis occurs as perennial vasomotor rhinitis and as acute rhinitis during attacks of rhinorrhea associated with headache and lacrimation [2]. SM patients do not characteristically have increased lung symptoms due to media-

tor release and postmortem findings confirm the lack of increase in pulmonary mast cells [4]. One patient described as having UP, mast cell granulomas and reticular infiltration of the lungs on chest x-ray experienced spontaneous acute attacks of bronchospasm [35]. Patients with MCL can present lung mast cell infiltration [4].

### Pregnancy

Pregnancy is associated with multiple endocrine changes, including increased levels of progesterone and prolactin during lactation. Limited studies are available on patients with mastocytosis and pregnancy. From 8 women with ISM who gave birth to 11 healthy children, one third had mild exacerbations of their symptoms during pregnancy. No adverse reactions during anesthesia were observed and no complications occurred during labor and delivery [36].

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