

Mast Cell Mediators of Significance in Clinical Practice in Mastocytosis



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KEYWORDS

- *N*-methylhistamine • 2,3-dinor-11 β Prostaglandin(PG) F2 α • Leukotriene(LT) E4
- Tryptase • Histamine • Neuropeptide

KEY POINTS

- Mast cells are known to store and secrete a variety of mediators; however, it is not possible for clinical laboratories to measure most of them.
- Although several mast cell mediator metabolites are measured in the urine, aside from serum tryptase measurement no other mast cell mediator is included in diagnostic criteria for systemic mastocytosis.
- By quantitating an increase in one or more mast cell mediators coincident with acute symptoms and comparison with baseline values, evidence of mast cell participation in clinical syndromes is verified.
- Emerging evidence suggests that various cytokines and neuropeptides may have clinical relevance in systemic mastocytosis.

INTRODUCTION

The local and/or remote symptoms that result from mast cell (MC) mediator release are common reasons that patients with systemic mastocytosis (SM) seek medical care. Documentation of an increase in the level of one or more MC mediators, obtained at baseline or during acute symptom flares, serves to confirm the participation of these cells in the pathogenesis of a clinical condition. However, the clinical laboratory's ability to routinely measure MC mediators day-to-day is severely limited.

MCs and their mediators have been hypothesized to participate in a great number of disorders and to contribute to the pathogenesis of clinical conditions outside that of SM.¹

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MCs are induced to activate by IgE-triggered stimuli and non-IgE causes including hormones, complement fragments, physical factors, immunoglobulins, toll-like receptor ligands, pathogens and their components, antimicrobial peptides, neuropeptides, toxins, cytokines and other inflammatory mediators, chemokines, other chemoattractants, and exogenous molecules and drugs.^{2,3} However, aside from the physical presence of increased numbers of MC infiltrating tissue it is difficult to substantiate a primary contribution of MCs in a legion of disorders ranging from chronic bronchitis to chronic fatigue syndrome⁴ using currently available tests to quantify MC mediators.

Hardly a month goes by in which new factors or pathways affecting MC degranulation are not reported. Many of these reports come from studies in nonhuman species or from in vitro studies that may use nonhuman MCs. The applicability of these reports to the clinical practice of diagnosing and managing patients with SM is frequently unproven.

MCs are factories for the production of mediators that are released immediately or in a delayed fashion. These products have proinflammatory, immunomodulatory, or chemokine effects that in turn can impact other immune cells in the body and stimulate the production of inflammatory mediators by these cells. In SM, the greatly increased number of MCs has the potential to magnify the results from mediator release. Furthermore, production of mediators by MCs themselves is affected by exposure to other inflammatory products.⁵ These observations suggest a complex web of interacting systems affecting MC mediator secretion.

Rather than being a compendium of MC products, this article is focused on those MC mediators with current or potential relevance to the management of patients with SM. It is hoped that this serves as a useful resource to clinicians for evaluation and management of these patients.

PREFORMED MEDIATORS

Biologic Amines

Histamine

Histamine (2-[4-imidazolyl]-ethylamine) is an endogenous amine that is synthesized by histidine decarboxylase, which removes a carboxylic acid residue from the semiesential amino acid L-histidine. Histamine may be produced by a wide variety of cell types that express histidine decarboxylase including MCs, basophils, gastric enterochromaffin-like cells, histaminergic neurons, platelets, dendritic cells, and lymphocytes. MCs and basophils store large quantities of histamine in secretory granules, whereas other cell types, such as lymphocytes, secrete histamine after synthesis and do not store it intracellularly. MCs and basophils release histamine on degranulation in response to immunologic and nonimmunologic stimuli.^{6,7}

Once released, histamine is metabolized rapidly (half-life of 1 minute) via two enzymatic pathways. Most histamine is metabolized by histamine *N*-methyltransferase (HNMT), which is an S-adenosyl-methionine-dependent enzyme responsible for 70% to 80% of histamine biotransformation. HNMT acts as a catalyst for the transfer of a methyl group from S-adenosyl-L-methionine to histamine, resulting in the formation of *N*-methylhistamine. *N*-Methylhistamine is then metabolized further by monoamine oxidase to *N*-methylimidazole acetic acid, which is then excreted in the urine.^{7,8} HNMT is found in tissues throughout the body and is particularly important in the central nervous system and bronchial epithelium, where it is the only known metabolic process to inactivate histamine.⁷

The second enzymatic pathway metabolizing the remaining 20% to 30% of histamine occurs through the activities of diamine oxidase. Diamine oxidase is a membrane glycoprotein that is mainly found in the kidney and colon. Diamine oxidase is stored in

plasma membrane vesicles and is released on stimulation to oxidatively deaminate histamine and other substrates. Diamine oxidase converts histamine to imidazole acetaldehyde, which is then subsequently converted to imidazole acetic acid and conjugated with ribose phosphate.^{7,8}

Histamine induces widespread responses and plays important physiologic roles in human health.^{7,9} Histamine exerts its diverse effects via binding to four subtypes of histamine receptors (HRs), which are named chronologically in order of their discovery (H1R to H4R).⁶

H1R-mediated effects include itching, swelling, rhinorrhea, conjunctivitis, urticaria, bronchoconstriction, and anaphylaxis. In addition, H1R may have centrally mediated effects affecting attention, sleep regulation, and regulation of food and water intake.⁶

H2R activation results in relaxation of smooth muscle in the airway and vasculature. H2R-mediated effects are most discussed in relation to gastric acid secretion, because occupation of parietal cell H2R results in hydrogen ion production. H2R activation may also be involved in regulation of gastric motility, and in the cardiovascular system, may induce negative chronotropic and ionotropic effects.⁷

H3R inhibits histamine release from histaminergic neurons in the human brain and also seems to be involved in the regulation of the release of neurotransmitters, such as dopamine, serotonin, noradrenaline, γ -aminobutyric acid, and acetylcholine in the human brain.⁷ Thereby, H3R is shown to be important in the sleep-wake cycle, cognition, homeostatic regulation of energy levels, and inflammation.⁶ H4R is emerging as an important receptor for chemotaxis and modulation of inflammatory responses.⁶

Overproduction of histamine in SM has been reported for more than 30 years, but histamine levels in blood or urine are not used in current diagnostic criteria. In patients with SM, plasma histamine levels demonstrate a diurnal variation with highest levels observed in the early morning. Although patients with SM have elevated plasma histamine levels on average, the determination of such levels has not proven to be reliable to screen patients for mastocytosis.¹⁰ However, measurement of the urinary histamine metabolites *N*-methylhistamine and *N*-methylimidazole acetic acid, rather than measurement of urinary histamine, has been shown to correlate with serum tryptase levels and bone marrow biopsy findings in multiple studies.^{11–14} In addition, urinary histamine metabolite measurements have been included in diagnostic algorithms proposed by the European Competency Network on Mastocytosis and other groups to select patients for bone marrow examination to establish a diagnosis of SM.¹²

In one study involving 37 patients with elevated levels of urinary *N*-methylhistamine, the optimal predictive value for detecting MC aggregates in the bone marrow biopsy was an *N*-methylhistamine level of 297 $\mu\text{mol/mol}$ creatinine (Cr) at which the sensitivity was 67% with a specificity of 84%. Another study involving 161 different patients demonstrated a significant correlation between serum tryptase and urinary *N*-methylhistamine levels. Of these 161 patients, 13 patients had retrievable bone marrow biopsies, and significant differences were found for serum tryptase and urinary *N*-methylhistamine levels between bone marrow biopsies with an increased number of MC aggregates and those without such increases. It was noted, however, that serum tryptase discriminated better than urinary *N*-methylhistamine between patients with and without increased MC aggregates in bone marrow biopsies.¹³

A more recent study¹² involving 142 patients undergoing evaluation for mastocytosis included 53 patients without urticaria pigmentosa who were diagnosed with indolent SM (ISM) and 89 patients who ultimately were not diagnosed with mastocytosis. In this study, when tryptase levels were greater than 10 $\mu\text{g/L}$, the highest combination of sensitivity and specificity for a diagnosis of SM was 2.0 mmol/mol Cr for methylimidazole acetic acid (sensitivity, 0.85; specificity, 0.86) and 176 $\mu\text{mol/mol}$ Cr for

methylhistamine (sensitivity, 0.81; specificity, 0.93).¹² One final study¹⁴ involving 90 patients found that urinary *N*-methylhistamine levels positively correlated with serum tryptase levels and the percentage of MCs on bone marrow biopsy. There was also a significant difference of urinary *N*-methylhistamine levels between subjects found to have atypical MCs on bone marrow biopsy and those who did not. Furthermore, urinary *N*-methylhistamine levels were statistically different between the patient group positive for *c-kit* mutation versus the group that lacked the mutation. It was also noted that as urinary *N*-methylhistamine levels increased, greater proportions of patients demonstrated the aforementioned associated correlations. Thereby, this study found that a urinary *N*-methylhistamine level that is twice the upper limit of normal (400 $\mu\text{g/g}$ Cr), corresponds to 95% MC atypia and 85% MC aggregates on bone marrow biopsy, and thus may be clinically useful to predict bone marrow findings in SM.¹⁴ In summary, several investigations of urinary histamine metabolites have demonstrated clear utility to aid SM evaluation and diagnosis, and evolving diagnostic criteria for SM may reflect the measurement of urinary *N*-methylhistamine levels in the future.

Chemokines

Chemokines are low-molecular-weight chemotactic cytokines divided into four main families depending on the position of conserved cysteine residues near the N terminus. Cultured MCs produce the chemokines monocyte chemotactic protein-1¹⁵ and interleukin (IL)-8.¹⁶

Interleukin-8

IL-8 (CXCL8) is produced by many cell types including MCs. Clinically, significant elevations of IL-8 serum levels are found in patients with interstitial cystitis/bladder pain syndrome.¹⁷ Among a cohort of 46 patients with ISM, aggressive SM (ASM), and SM with associated clonal hematopoietic disorder (SM-AHN) a panel of assayed cytokines showed only IL-8 levels to be significantly different in SM-AHN versus ISM/ASM patients ($P < .0002$).¹⁸ A clinical study of patients with SM demonstrated that serum IL-8 and monocyte chemotactic protein-1 were significantly elevated in patients with anaphylaxis versus patients without anaphylaxis.¹⁹

Enzymes

Tryptase

Tryptase is the most specific marker of MC activation and burden. Tryptase is a serine protease concentrated in the secretory granules of all MCs. Basophils also have a negligible amount of tryptase, about 0.4% of that of MCs.²⁰

Tryptase has multiple biologic activities. Tryptase promotes tissue repair and generates bradykinin from kininogen leading to increased vascular permeability and facilitating cellular migration. Tryptase has chemotactic effects on neutrophils and eosinophils via release of IL-8. It upregulates ICAM-1 expression on epithelial cells. Tryptase is a growth factor for epithelial cells, respiratory smooth muscle cells, and fibroblasts.²¹ Tryptase-mediated degradation of bronchodilators vasoactive intestinal peptide and peptide histidine-methionine seems to contribute to bronchial hyperresponsiveness and the decrease in immunoreactive vasoactive intestinal peptide in airway nerves associated with asthma.²²

Tryptase cleaves α and β chains of fibrinogen. Thrombin-initiated clot formation is thereby inhibited.²³ The anticoagulant activity of β tryptase can partially explain the bleeding episodes in patients with SM and anaphylaxis.

α -Pro-tryptase is the predominant form of tryptase in serum at baseline in normal subjects and in those with SM. β -tryptase is the predominant form from MCs in skin

and lung and in the blood during systemic anaphylaxis. Release of β -tryptase parallels histamine but diffuses more slowly because it is associated with protease-proteoglycan complex. β -tryptase peaks at 30 to 90 minutes following MC activation or an anaphylactic event, with a half-life of 2 hours, whereas histamine peaks at 5 minutes and returns to baseline within 15 to 30 minutes. Thus, optimal time to obtain tryptase is 1 to 2 hours after precipitating event.²⁴

Total MC tryptase (α - and β -tryptases) reflect the total MC burden. The normal tryptase level in adults is 1 to 15 ng/mL, with average of 5 ng/mL. A serum level greater than 11.5 ng/mL, the 95th percentile, is considered increased. The median tryptase level in children is 3.30 ng/mL (range, 2.38–4.36) and is inversely related to age.²⁵ There is one currently available blood tryptase assay (Phadia Laboratory Systems, Uppsala, Sweden), performed via fluorescence enzyme immunoassay. This assay does not distinguish between α - and β -tryptases.

Higher tryptase levels increase the likelihood of SM. Serum tryptase greater than 20 ng/mL is one of the minor criteria of SM. Tryptase levels vary among forms of SM. Highest levels are detected in MC leukemia and smoldering SM, compared to isolated bone marrow (no cutaneous or multi organ involvement).²⁶ Also, in ISM-suspected patients greater than 50 years with a body mass index greater than 25 kg/m², there is diminished reliability of tryptase as risk indicator for mastocytosis.²⁷

Elevation of tryptase is not specific to SM. Elevation of tryptase has also been seen in systemic anaphylaxis, acute myelocytic leukemia, various myelodysplastic syndromes, hypereosinophilic syndrome associated with the FLP1L1-PDGFR mutation, end-stage renal failure, treatment of onchocerciasis, and familial hypertryptasemia. Among patients with myeloid neoplasm, blood tryptase greater than 15 ng/mL was found in greater than 90% of SM cases, 38% of acute myelocytic leukemia, 34% of patients with chronic myelogenous leukemia, and 25% of patients with myelodysplastic syndrome. A corollary of these observations is that serum tryptase levels cannot be used as a minor criterion when diagnosing SM in those patients with an associated hematologic neoplasm. Serum tryptase levels do not correlate with therapy-induced bone marrow complete response at a given single time point.²⁸ Also, non-SM obese individuals were found to have elevated tryptase. Detecting elevated baseline serum tryptase levels in individuals who experienced anaphylaxis to a stinging insect can indicate underlying SM.

In contrast to ASM, patients with ISM usually present with urticaria pigmentosa-like skin lesions. Lack of these lesions does not exclude ISM even if the serum tryptase is elevated. Increasing tryptase levels in patients with ISM is associated with poor prognosis and increased progression. Patients with SM have increased risk for decreased bone density and pathologic fractures; however, elevated tryptase levels are actually associated with greater bone density in a cohort of patients with SM. Patients with SM with less severe disease and lower serum tryptase levels should particularly have bone density evaluated.

Children Increased tryptase levels were also found in children with systemic disease and correlated to skin lesion density and bone marrow pathology. In children with extensive cutaneous involvement, increased serum baseline tryptase identifies patients at risk for severe MC activation events in pediatric mastocytosis. In cutaneous mastocytosis organomegaly was the strongest predictor of SM, whereas serum tryptase values alone were not predictive in the determination of systemic involvement. Sequential tryptase measurements, however, were helpful in supplementing clinical judgment as to disease course.²⁹ **Table 1** lists a selection of preformed MC mediators whose contribution to acute and/or chronic symptoms in SM remains to be fully validated.

Table 1 Mast cell enzymes of possible, but unproven, clinical significance in mastocytosis		
Mast Cell Mediator	Action	Reference
Carboxypeptidase A	• Skin MCs have greater content than lung MCs • Selectively localized to tryptase-positive, chymase-positive MCs • Increased in children with allergic disease	Pan et al, ³⁰ 2011
Chymase	• Indolent mastocytosis patient revealed tryptase-positive, chymase-positive MCs in skin and bone marrow	Weidner et al, ³¹ 1992
Kininogenase	• Released via IgE-mediated mechanism • Kinin formation	Proud et al, ³² 1985
Metalloproteinase-9	• Mast cell migration into tissues	Tanaka et al, ³³ 1999
Peroxidase	• Found in mast cells in urticaria pigmentosa • Appearance associated with cells' ability to synthesize PGD₂ • Marker of in vitro maturation of bone marrow-derived mast cells	Akiyama et al, ³⁴ 1989
Arylsulfatase, nitric oxide synthase, nitric oxide, phospholipase, β -hexosaminidase	• Limited animal studies	

Proteoglycans

Chondroitin sulfate

Mast cell granules contain the proteoglycan serglycin, which has glycosaminoglycan side chains of negatively charged heparin, chondroitin, or dermatan sulfate.³⁵ These proteoglycans are responsible for the metachromatic staining of MCs and serve as storage sites for positively charged proteases.³⁶ Although chondroitin sulfate when preincubated with LAD2 human MCs inhibits substance P-induced IL-8 and tumor necrosis factor release, there are no studies implicating chondroitin sulfate in the pathophysiology or clinical symptoms of SM.

Heparin

Human MC granules contain the highly sulfated proteoglycan heparin (5 pg/10⁶ cells).³⁷ Heparin and chondroitin sulfate diB/E containing serglycin proteoglycans are located within the electron dense MC secretory granules. By binding to antithrombin heparin induces a conformational change in antithrombin that greatly enhances its anticoagulant activity through inactivation of thrombin and factor Xa.³⁸

Serglycin proteoglycans also bind and stabilize tetramer-forming tryptases in MC secretory granules and are essential in maintaining activity of human tryptase- β to cleave the α and β chains of human fibrinogen thereby inhibiting clot formation.³⁹ An elevation of the plasma heparin level, particularly after stimulation of MC degranulation by obstruction of venous flow for 10 minutes, has been proposed as a marker for MC activation disorder,⁴⁰ but has not been evaluated in SM. In one series clinical signs of bleeding including hematoma formation, bruising, prolonged bleeding after biopsies, gingival bleeding, epistaxis, gastrointestinal, and other were reported in

patients with MC activation disorder.⁴¹ In SM bleeding is not a commonly reported problem. There are only occasional reports of clotting abnormalities related to MC degranulation⁴² and/or organ infiltration by MCs in patients with SM-AHN⁴³ or MC leukemia.⁴⁴

DE NOVO MEDIATORS
Phospholipid Metabolites

Prostaglandins

Prostaglandin (PG) D₂ is a lipid-derived MC mediator that is rapidly degraded into D-, F-, and J-ring metabolites, which are excreted as more stable urinary metabolites (Fig. 1). Mast cells, not basophils, remain the predominant source of PGD₂. patients with SM excrete four times more PG-F-ring compared with PG-D-ring metabolites. The predominant clinically measured urinary metabolite is 2,3-dinor-11 β prostaglandin F2 α (2,3-BPG) (Fig. 2).

Multiple studies have shown elevated urinary excretion of PGD₂ in SM. A patient treated with antihistamines and aspirin, 975 mg orally four times a day, for 8 months had reduced excretion of PGD₂ metabolite by 80% to 85% and symptom reduction.

PGD-M is a downstream metabolite of PGD₂. Measurement of urine PGD-M was increased greater than normal by 300% in patients with SM.⁴⁵ PGD-M is measured

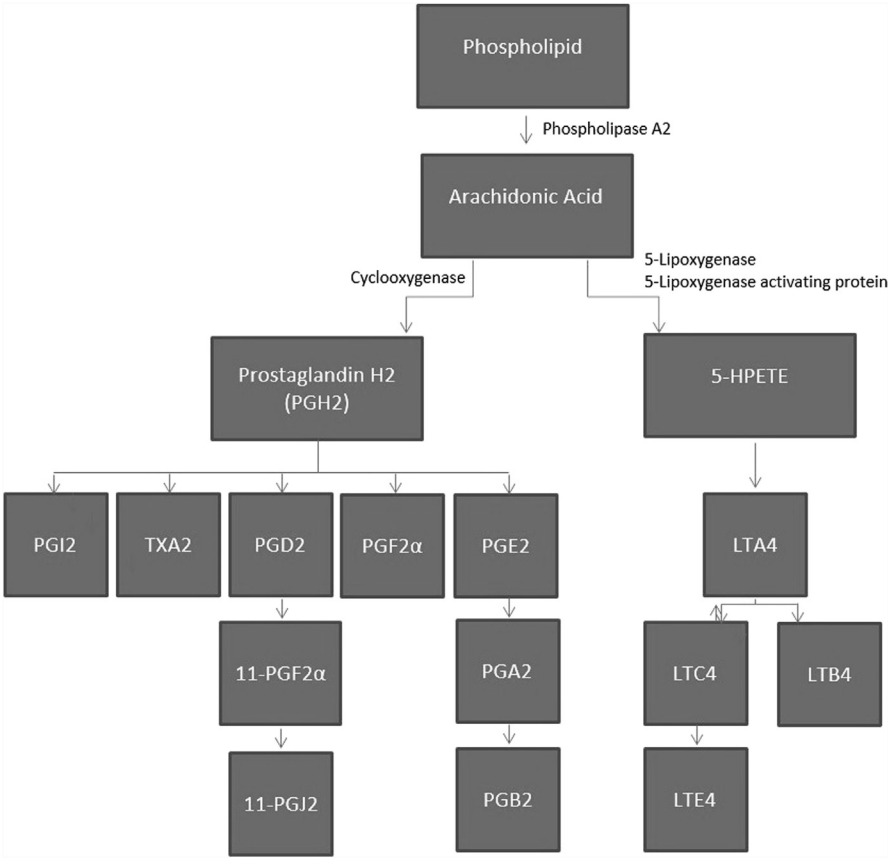


Fig. 1. Arachidonic acid metabolism.

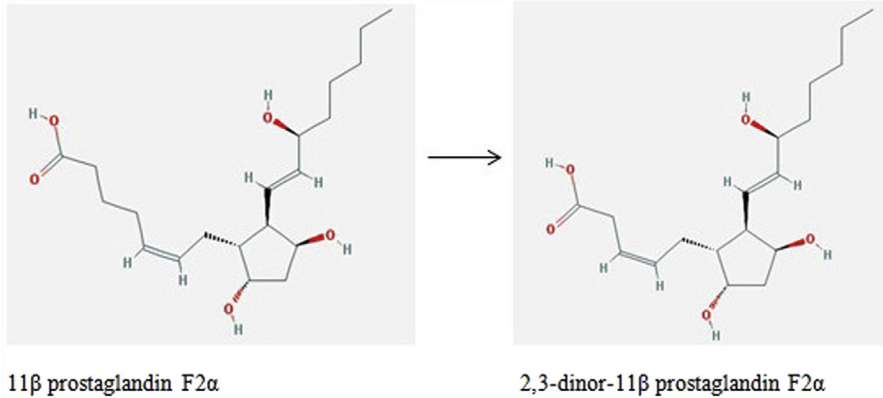


Fig. 2. Prostaglandin F-ring. (From National Center for Biotechnology Information. PubChem Compound Database; CID = 5280886. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/5280886>. Accessed November 17, 2017; and National Center for Biotechnology Information. PubChem Compound Database; CID = 5283032. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/5283032>. Accessed November 17, 2017.)

by gas chromatography compared with the measurement of 2,3-BPG, which uses liquid chromatography and tandem mass spectrometry. Mean urinary excretion of PGD-M was significantly higher ($P < .01$) in patients with SM compared with control subjects (37.2 vs 11.5 ng/mg Cr) with 65% of 17 patients with SM showing elevated levels.⁴⁶

The clinical sensitivity of 11 β -PGF2 α (>1000 ng/mL) alone for diagnosis of SM was determined to be 53%.⁴⁷ In a Mayo Clinic study of 22 patients with SM, elevated urinary excretion levels of 11 β -PGF2 α greater than 3494 ng/24 hours correlated with the presence of bone marrow MC aggregates (89%) and atypical MC (100%) but not with c-kit positivity.¹⁴

Cysteinyl leukotrienes: leukotriene E4

Cysteinyl leukotrienes are mediators produced by activated MCs, neutrophils, eosinophils, and macrophages. Leukotriene C4 is a lipid mediator that is metabolized into leukotriene D4 and subsequently into leukotriene E4 (LTE4) (see Fig. 1). LTE4 is the primary stable metabolite of cysteinyl leukotrienes.

LTE4 is excreted in the urine, where it is assayed by liquid chromatography followed by tandem mass spectroscopy. Patients with SM have significantly increased excretion of LTE4 pg/mg Cr (median, 30 ng/g Cr; range, 3.0–188 ng/g Cr) compared with the control group (median, 7.0 ng/g Cr; range, 1.0–128 ng/g Cr; $P = .01$).⁴⁸

Median urine LTE4 among patients with SM was 97 pg/mg Cr, significantly higher than patients without SM 50 pg/mg Cr ($P < .01$). The 95th percentile of the reference interval population was less than 104 pg/mg Cr. The reference interval cutoff of 104 pg/mg Cr for LTE4 was 48% sensitive and 84% specific for a diagnosis of SM.⁴⁷

Platelet activating factor

Platelet activating factor (PAF) is produced by MCs, endothelial cells, polymorphonuclear leukocytes, eosinophils, macrophages, monocytes, and platelets. In allergic disorders, the source of PAF is antigen-stimulated basophils and MCs. PAF activates eosinophils and Polymorphonuclear leukocytes. PAF has been detected in blister fluid in a patient with bullous mastocytosis. In 1988, treatment of adult SM with a PAF-

acether antagonist BN52063 resulted in resolution of symptoms.⁴⁹ The role of PAF in the day-to-day symptoms of SM has yet to be elucidated. **Table 2** summarizes the symptoms caused by mast cell mediators that can be measured in clinical laboratories.

Cytokines

Human MCs have demonstrated the capability to synthesize and release several multifunctional cytokines including IL-1, IL-3, IL-5, IL-6, IL-13, IL-16, IL-18, IL-31, tumor necrosis factor- α , transforming growth factor- β , and macrophage inflammatory protein-1 α . These cytokines have physiologic effects primarily with inflammation and leukocyte migration and proliferation. Cytokines are typically synthesized de novo and are released several hours after MC activation. MCs may be activated via IgE- or IgG-dependent mechanisms or also in response to bacterial products through Toll-like receptors.^{50–54} Much of the data associating these cytokines with MCs were obtained from studies with human MC lines and primary MC cultures. Cytokine expression and regulation by resident tissue MCs in those with mastocytosis remain largely undetermined.⁵⁵ The limited number of cytokines that have been studied in SM include IL-6 and IL-31.

Table 2 Symptoms from mast cell–derived mediators routinely measured in clinical laboratories		
Mast Cell Mediator	Collection Method	Symptom
Histamine N-Methylhistamine	Urine	Headache Nasal obstruction/rhinorrhea/sneezing Hypotension Urticaria $\pm$ angioedema Pruritus Flushing Nausea/vomiting Diarrhea Abdominal pain
PGD ₂	Urine	Mucus secretion Bronchoconstriction Vascular instability/vasodilator Coronary and pulmonary vasoconstrictor Inhibition of platelet aggregation Eosinophil and neutrophil chemoattractant Dendritic cell activation Augmentation of basophil histamine release
2,3Dinor 11 β -PGF2 α PGD ₂ metabolite	Urine	Bronchoconstriction Peripheral vasodilation Coronary vasoconstriction Inhibition of platelet aggregation
LTE4	Urine	Bronchoconstriction Enhanced bronchial responsiveness Increased vascular permeability Mucus secretion Edema formation
Tryptase	Serum	Bleeding Bronchospasm Increased fibroblast proliferation and collagen synthesis
Heparin	Plasma	Bleeding

Interleukin-6

Of the cytokines studied in SM, IL-6 potentially has the most clinical relevance to date. IL-6 has been shown to be increased in SM with plasma levels correlating with disease severity and progression.^{55–58} Specifically, increased plasma IL-6 levels of patients with SM correlated with serum tryptase levels, symptom severity, aggressive disease category, severity of bone marrow pathology, organomegaly, hematologic abnormalities, presence of osteoporosis, and extent of skin involvement.^{55–57} Furthermore, plasma IL-6 levels greater than 2.5 pg/mL identified all patients with severe disease, aggressive disease categories, and all with organomegalies. Increased plasma IL-6 levels of this magnitude also identified more than 90% of patients with diffuse infiltrates found on bone marrow biopsy. These increased IL-6 levels were not found in control subjects or in patients with cutaneous mastocytosis.⁵⁶ Not only do IL-6 levels seem to be a useful surrogate marker for disease, IL-6 levels also have demonstrated prognostic significance. In patients with ISM, high levels of IL-6 were associated with disease severity, organomegalies, and disease progression to more aggressive disease.⁵⁸ These findings suggest that IL-6 blockade may be beneficial to lessen MC-related symptoms and pathology in patients with mastocytosis and increased IL-6 levels.

Interleukin-31

IL-31 seems to be a cytokine playing a key role in the induction of chronic skin inflammation. Increased serum IL-31 levels and increased IL-31 mRNA levels in the skin have been demonstrated in patients with atopic dermatitis, chronic urticaria, allergic contact dermatitis, prurigo nodularis, and primary cutaneous lymphomas.^{59–63} Sources of IL-31 include CD4⁺ T cells, CD45R0 CLA⁺ T cells, and MCs.⁵⁹ In one study, serum IL-31 levels were found to be significantly increased in patients with mastocytosis compared with that found in healthy control subjects.⁵⁹ Moreover, patients with more advanced disease categories, such as ASM, demonstrated significantly increased IL-31 levels compared with those with nonadvanced disease, such as cutaneous mastocytosis or ISM. All IL-31 levels exceeding 313.9 pg/mL were measured in patients with advanced disease categories, and none of the patients with advanced disease had IL-31 levels less than 81.9 pg/mL. In addition, IL-31 levels also correlated with serum tryptase levels and with the percentage of MC infiltrates in the bone marrow. In contrast, IL-31 levels did not correlate with other clinical parameters including disease duration; presence of a KitD816 V mutation; skin lesion involvement; or presence of MC activation symptoms, such as pruritus, flushing, or anaphylaxis. Through immunohistochemistry, MCs in skin and bone marrow were shown to be able to produce IL-31.⁵⁹ Thus, IL -31 levels may be another potential diagnostic biomarker for mastocytosis.

Growth Factors

Stem cell factor

The most important cytokine that contributes to MC differentiation and maturation is the ligand stem cell factor (SCF),⁶⁴ which binds to its specific tyrosine kinase receptor, *kit*, encoded by the *kit* proto-oncogene. Cardiac MCs from patients with idiopathic dilated cardiomyopathy were first shown to contain SCF in their secretory granules by immunogold staining. Subsequent studies using skin MCs and human lung MCs also demonstrated the presence of immunoreactive SCF.⁶⁵ Chymase, present in MC secretory granules, cleaves recombinant human SCF (SCF^{1–166}). The larger cleaved fragment, SCF^{1–159}, but not the minor cleavage product SCF^{159–166} activates human lung MCs, potentiates anti-IgE-induced activation of these cells, and

stimulates human lung MCs chemotaxis.⁶⁶ Specific clinical symptoms attributable to SCF apart from these effects on MCs have not been identified.

Nerve growth factor

Mast cells respond to and produce nerve growth factor (NGF), a unique neurotrophic factor with a wide range of biologic effects.⁶⁷ Patients with SM show elevated serum levels of NGF, neurotrophin (NT)-3, and NT4. Levels of NGF- β and NT4 also correlate with serum tryptase levels and expression of receptors for NT have been demonstrated on intestinal and skin MCs of patients with SM.⁶⁸ Although the release of NGF can contribute to the accumulation of MCs in inflammatory and autoimmune states, the specific contribution of this trophic factor to symptoms of patients with SM awaits further study.

SUMMARY

For diagnosing and treating SM the utility of quantitating levels of released MC mediators remains to be fully explored. Aside from tryptase, other MC products are not current criteria for diagnosing SM. Mediator levels are used to document excessive levels of released MC products present chronically or contemporaneously during MC activation events. By blocking the synthesis of these mediators or their receptors, relief of MC-induced symptoms is achieved (**Table 2**).

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