Systemic Mastocytosis

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Opinion statement

Systemic mastocytosis is a rare clinical disorder characterized by the proliferation of mast cells, which are commonly in the skin but may be found in other body sites as well. Mast cells contain chemically active substances that, on release, produce symptoms associated with the disease. The intent of this review is to provide some insight into the clinical nature of this disorder.

Introduction

The reported annual incidence of systemic mastocytosis is 0.3 new cases per 100,00 of the general population. The disease affects both sexes equally but is more prevalent in whites than in blacks. The onset, particularly with regard to the indolent form of the disease, occurs in about 55% of patients between birth and 2 years of age; another 10% develop symptoms between the ages of 2 and 15 years. The remaining 35% of patients develop symptoms after 15 years of age. The disease culprit is the mast cell, which is derived from the multipotent hemapoietic stem cell. Neoplasms of mast cells can be acute or chronic, with acute mast cell neoplasms designated primarily as mast cell leukemias. Chronic mast cell neoplasms, the category to which systemic mastocytosis belongs, may be localized or generalized. Cutaneous mastocytosis is the most common form of localized mast cell neoplasm, although cutaneous disease often has subclinical involvement of the bone marrow. Not all cutaneous mastocytoses are necessarily neoplastic. Childhood forms of the disease may be reactive and may occasionally remit. However, adult mastocytosis due to the frequent clonal cytogenetic and molecular genetic abnormalities is considered a neoplastic process [1•].

CLINICAL PRESENTATION

Systemic mastocytosis represents a general category of disease with a variety of clinical manifestations, each with different prognostic implications. Table 1 outlines the Metcalfe classification, which is the preferred categorization schema.

Category I represents indolent disease, a process that is invariably limited to the target organs affected. Clinically, indolent mastocytosis may appear in any number of clinical scenarios, which can include syncope, cutaneous disease, ulcer disease, malabsorption, skeletal disease, hepatomegaly, and lymphadenopathy. Hypersplenism has been documented to occur as well. Category I mastocytosis is by far the most common of the disease processes, and most patients are treated successfully without any decrease in lifespan. The most typical skin lesions are those of urticaria pigmentosa, which is a reddish, macular rash derived from the presence of mast cells in the skin. Proliferation in bone produces pain, and mastocytosis-induced osteoporosis has been described. Malabsorption may occur owing to increased mast cell load in the small intestinal wall. In the liver, there may be mast cell infiltration in the portal tract and sinusoids. In this setting, a minority of patients have been reported to develop nodular regenerative hyperplasia, veno-occlusive disease, cirrhosis, and portal hypertension in the absence of cirrhosis.

A distinction must be made between systemic symptoms and systemic disease. Patients with only skin manifestations may have systemic symptoms, as well as other indolent infiltrative manifestations of the disease. The systemic affect is thought to be secondary to histamine and prostaglandins released from secretory granules. These mediators account for the flushing, pruritus, headaches, and bronchospasm, as well as gastric manifestations of the disease, such as vomiting and diarrhea. Some patients have a coagulation defect secondary to the release of heparin. Mast cells also release other membrane-derived lipid mediators beside prostaglandins, such as leukotrienes and platelet-activating factor, in addition to inflammatory cytokines, such as interferon, tumor necrosis factor, and interleukins 1, 3, 4, 5, and 6. Emotional disturbance, exposure to heat, alcohol, aspirin, anticholinergics, nonsteroidal anti-inflammatory drugs, and contrast media may precipitate release of mast cell granules.

Table 1. Metcalfe classification of mast cell neoplasms

Category IA	Indolent disease confined to skin
Category IB	Indolent systemic disease with or without cutaneous involvement
Category II	Mastocytosis with an associated hematologic disorder
Category III	Aggressive lymphadenopathic mastocytosis with eosinophilia
Category IV	Mastocytic leukemia

DIAGNOSIS

When there is clinical suspicion of the disease, diagnostic studies should be directed toward presentation and may include a skin examination (gross and microscopic), bone marrow biopsy and aspiration, 24-hour urinalysis to uncover mediators, and a bone scan or skeletal survey. Measurement of serum tryptase may be a useful diagnostic tool as well.

Gastrointestinal work-up may be sufficient for the primary diagnosis; studies such as upper endoscopy and colonoscopy with biopsies should be considered in the appropriate setting. On endoscopy, the mucosa produces a whitish, velvety appearance secondary mast cell infiltration [2•].

The diagnosis of systemic mastocytosis (Table 2) can be difficult, particularly if the clinical presentation does not reveal conspicuous features, such as those seen in patients giving a history of only night sweats, abdominal pain, and diarrhea. Also, one should be alert to patients who present a clinical picture that may be defined as "essential thrombocythemia" or "hypereosinophilic syndrome." The disease should be considered when examining the bone marrow biopsy in these settings. Giemsa and chloroacetate esterase stains are of benefit when assessing histologic sections. The development of monoclonal antibodies to mast cell tryptase has been a welcomed diagnostic advance in this setting.

The natural history of indolent mastocytosis in adults is relatively unknown, although there are data to suggest that with the level of urinary excretion of histamine metabolites thought to reflect the mast cell load, clinical signs and symptoms of indolent mastocytosis can substantially decline, especially in older patients.

Metcalfe category II consists of mastocytosis associated with myeloproliferative or myelodysplastic disease. Metcalfe category III is an aggressive variant of mastocytosis that progresses from the bone marrow to the gastrointestinal tract, liver, spleen, and lymph nodes. Eosinophilia has been noted in 2% to 40% of patients

Table 2. Therapy of mastocytosis

Antihistamine
Corticosteroids
Nonsteroidal anti-inflammatory drugs
Disodium cromoglycate

with systemic mastocytosis, with eosinophils commonly accompanying mast cells in tissues. These manifestations support the myeloproliferative nature of this condition. Adding evidence to the clonal nature of systemic mastocytosis is the frequent finding of clonal molecular and cytogenetic abnormalities in these mast cell populations. Prognostic features for both category II and category III depend strongly on the associated hematologic disorder, with category III having a much more guarded prognosis.

Metcalfe category IV is mast cell leukemia that can present de novo or as the terminal phase of systemic mastocytosis. Most often, the leukemia is acute myeloblastic or myelomonocytic, although other types have been reported. Besides the clinical features usually ascribed to acute myeloid leukemia, there may be the added features resulting from release of mast cell granules, for example, flushing, peptic ulceration, and diarrhea. The peripheral blood shows mast cells that are often immature or morphologically abnormal. The bone marrow is hypercellular and heavily infiltrated by mast cells. The most specific mast cell marker is mast cell tryptase. The prognosis in patients with disease classified as Metcalfe category IV is usually death several months after the initial diagnosis.

Molecular genetic analysis in mast cell neoplasia reveals clonality in systemic mastocytosis demonstrable by either X-linked polymorphisms or detection of somatic mutations. The molecular lesions specific for mastocytosis are mutations in *c-KIT*, the gene for stem cell factor receptor as well as the cell-surface transmembrane receptor. KIT has tyrosine kinase activity and is the protein product of the *KIT* proto-oncogene. In several patients, the mutation of *c-KIT* has been associated with constitutive activation and postulated to be the stimulus behind abnormal mast cell proliferation. The data suggest that mutations in *c-KIT* are oncogenic in vivo, leading to stem cell factor–independent growth of mast cell precursors.

SUMMARY

Major advances have been made in our understanding of this rare disorder. It is hoped that current molecular and immunologic insights will point toward improved diagnostic and treatment options in the future.

Treatment

- The treatment of systemic mastocytosis is usually symptomatic owing to the indolent nature of the disease. There are instances, however, of life-threatening cardiovascular collapse [3••].
- Treatment is based on the combination of H_1 and H_2 histamine antagonists. H_1 antagonists relieve pruritus and flushing. Hydroxyzine and doxepin are two useful H_1 antihistamines; doxepin is particularly useful in patients who have central nervous system manifestations of mast cell disease. H_2 antagonists such as ranitidine or famotidine are often beneficial in improving gastrointestinal symptoms.
- Stabilization of mast cell membranes using sodium chromoglycate may reduce headaches, bone pain, diarrhea, and abdominal pain.
- Nonsteroidal anti-inflammatory agents arrest severe flushing and may be useful in preventing episodes of vascular collapse by preventing synthesis of prostaglandin D_2 within mast cells. However, caution is warranted because some nonsteroidal anti-inflammatory drugs (in particular, aspirin) may precipitate release of mast cell granule contents. Thus, it has been recommended that the drug, if used at all, should be started at a low dose and cautiously increased. Maximum dosing with antihistamines should be established before treatment. Anticholinergic agents, which are used in the treatment of diarrhea, may precipitate mast cell release. Patients prone to episodes of acute cardiovascular collapse may best be advised to carry epinephrine for self-administration. Finally, patients with mastocytosis-mediated osteoporosis and pathologic fractures may benefit from biphosphonates.
- Systemic corticosteroids have been used in some patients with mastocytosis. Although the treatment does control some symptoms, it does not appear to have an impact on the number mast cells. Corticosteroids have been demonstrated to decrease malabsorption and ascites in some patients with these problems secondary to systemic mastocytosis. With time, however, the ascites frequently reaccumulates. It has been suggested that these patients might benefit from portal caval shunts.
- Besides limiting mast cell release, benefit may also be derived from the control of mast cell proliferation. Treatment with interferon alpha-2b has lead to increase in hematologic cells in the bone marrow with a commensurate decrease in infiltration by mast cells. Although some studies demonstrate a remarkable response in the treatment of aggressive mastocytosis, others show no effectiveness in preventing the progression of disease. Further study is warranted in order to identify patients that might benefit from interferon treatment.
- Radiotherapy may be of use in some patients to control local disease. Splenectomy has been performed on some patients with aggressive mastocytosis in order to improve cytopenias.
- Recently, with the development of selective tyrosine kinase inhibitors such as imatinib mesylate, new treatments may be forthcoming. Recent data suggest efficacy of KIT receptor inhibitors in the treatment of gastrointestinal stromal tumors and chronic myeloproliferative diseases. Whether such results translate into treatment options for systemic mastocytosis will depend on future studies.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Pauls J, Brems J, Pockros PJ, *et al.*: **Mastocytosis: diverse presentations and outcomes.** *Arch Intern Med* 1999, **159:**401–405.

The authors review some of the more unusual manifestations of the disease.

2.• Scolapio JS, Woodward TA: **Endoscopic findings in systemic mastocytosis.** *Gastrointest Endosc* 1996, **44:**608–610.

This article documents with photographs the endoscopic appearance of the disease.

3.•• Marone G, Spadaro G, Granata F, Triggiani M: **Treatment of mastocytosis: pharmacologic basis and current concept.** *Leuk Res* 2001, **25:**583–594.

Overall, this review presents a nice overview of the interface between physiology and phamacology in systemic mastocytosis.