Mastocytosis

Melody C. Carter, MD, Dean D. Metcalfe, MD,
Hirsh D. Komarow, MD*

KEYWORDS

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

KEY POINTS

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

INTRODUCTION

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

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Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892, USA
* Corresponding author. Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 10, Room 1C129A1, 10 Center Drive, Bethesda, MD 20892-1960.
E-mail address: komarowh@niaid.nih.gov

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Mastocytosis has been classified into disease variants, which are listed in **Box 1** according to a World Health Organization (WHO) consensus.[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. 1**) is the least severe systemic variant, and patients with ISM or isolated CM are generally managed long-term with symptomatic therapies. Other forms with more severe manifestations carry a poorer prognosis and include systemic mastocytosis with an associated clonal, hematologic non–mast-cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL) and mast cell sarcoma. Of these forms, MCL, although rare, is the most aggressive and may be characterized by the presence of immature mast cells in peripheral blood.

CAUSES AND PATHOGENESIS

Mast Cell Origin, Growth, and Development

Human mast cells develop from $CD34^+$ 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 close to blood vessels, nerves, and glandular structures. They are particularly numerous in the skin, GI tract, respiratory tract, and lymphoid tissue. Mast cells have cytoplasmic granules that contain histamine and a multitude of other inflammatory mediators. Mature mast cells are long lived and tend to have a limited ability to differentiate.[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*, which encodes for KIT, have been detected in the bone marrow as well as skin and peripheral blood cells in patients with mastocytosis. The most common somatic mutation,

Box 1
World Health Organization classification of mastocytosis

- CM
  - Urticaria pigmentosa = maculopapular CM
  - DCM
  - Mastocytoma of skin
- ISM
  - Smoldering systemic mastocytosis
  - Isolated bone marrow mastocytosis
- Systemic mastocytosis with associated clonal, hematologic non–mast-cell lineage disease
- Aggressive systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytoma