New Insights into Clonal Mast Cell Disorders Including Mastocytosis

Sofija Volertas, MD[1], Charles F. Schuler IV, MD[1], Cem Akin, MD, PhD*

KEYWORDS

• Mastocytosis • Mast cell • Clonal mast cell disorders
• Monoclonal mast cell activation syndrome • Mast cell leukemia • Mast cell sarcoma
• Tryptase

KEY POINTS

- Mastocytosis is a heterogeneous grouping of neoplasms with clonal expansion of mast cells in one or more organ systems, typically including the skin and hematopoietic system.
- Systemic mastocytosis consists of a multifocal infiltration of mast cells into various organs, including the bone marrow.
- The diagnosis of mastocytosis requires tissue confirmation. Diagnostic algorithms have been established to guide the approach to patients with suspected mastocytosis.
- The mainstays of therapy for mastocytosis are symptomatic management, prevention of complications, and cytoreductive therapies for advanced disease.

Mast cells are an integral cell in the immune system, and disorders of regulation of mast cell production and activation have various presentations. Mastocytosis is a heterogeneous grouping of neoplasms with clonal expansion of mast cells in one or more organ systems, typically including the skin and hematopoietic system.[1–3] Mast cells are not found in the blood under normal circumstances but rather are present in most tissues. Abnormal mast cell expansion in clonal mast cell disorders tends to be focused in the skin, bone marrow, spleen, lymph nodes, and gastrointestinal tract, causing symptoms related to mast cell degranulation and less frequently symptoms of

Disclosure Statement: Dr C. Akin has consultancy agreements with Novartis, Blueprint Medicines, and Deciphera. Dr S. Volertas and Dr C.F. Schuler have no conflicts to report.

Division of Allergy and Clinical Immunology, Department of Internal Medicine, University of Michigan, 24 Frank Lloyd Wright Drive, PO Box 442, Suite H-2100, Ann Arbor, MI 48106-0442, USA
[1] Co–first authors.
* Corresponding author.
E-mail addresses: cemakin@med.umich.edu; cemakin@umich.edu

Immunol Allergy Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.iac.2018.04.014
immunology.theclinics.com

organ dysfunction. Mast cell activation can cause various symptoms in all organ systems, such as cardiovascular (hypotension, syncope, light-headedness, tachycardia), cutaneous (flushing, pruritus, urticaria, angioedema), digestive (abdominal cramps, diarrhea, esophageal reflux, nausea and vomiting), musculoskeletal (aches, bone pain, osteopenia and osteoporosis), neurologic (anxiety, depression, decreased concentration and memory, insomnia and migraines), respiratory (nasal congestion, nasal pruritus, shortness of breath, throat swelling, and wheezing), and systemic (fatigue, general malaise and weight loss).[4] Notably, there is an increased risk of anaphylaxis in patients with mastocytosis; this risk is higher in males, in the absence of mastocytosis in the skin, presence of atopy, immunoglobulin E (IgE) levels of 15 kU/L or greater, and baseline tryptase levels less than 40 ng/mL.[5]

Significant advancements over the past decade in understanding the cause, prognosis, diagnosis, and potential targets for treatment changed the understanding of mast cell disease and, thus, can guide physicians in appropriate care of patients with clonal mast cell disorders.

HISTORICAL PERSPECTIVE

The first urticaria pigmentosa (UP) lesion was described by Nettleship and Tay[6] in 1869, and mast cells were discovered by Paul Ehrlich in 1879.[1] A short 8 years later, it was noted that mast cells were present in these UP lesions by Paul Unna[7] in 1887. However, systemic disease was not described for another 60 years until Ellis[8] in 1949. There were further categories described; the modern criteria for diagnosis were established in the 2000s, with the World Health Organization's (WHO) first classification in 2001.[9] In 2016, the WHO adopted changes to these categories of mastocytosis and have brought us to our current state of understanding.

CLASSIFICATION OF CLONAL MAST CELL DISORDERS AND WORLD HEALTH ORGANIZATION'S RECENT UPDATES

The WHO's previous classification of mast cell disorders from 2001 focused on dividing mast cell disorders into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and solid mast cell tumors.[9] This framework has remained the same, with changes within the individual categories to reflect increasing knowledge of prognosis (**Box 1**). Notably, extracutaneous mastocytomas as a category were removed, as this is so rare and very few cases have been described in the past 20 years.[10]

Localized Mast Cell Tumors

Mast cell sarcomas (MCS) are extremely rare and remain as a separate category. There have been various reports of localized MCS that were present intracranially,[11] in the lung,[10] in the larynx,[12] and in the colon.[13] However, the data are too scarce to make any clear prognostic statement. Usually, MCS transform into a form of SM called mast cell leukemia (MCL).

Cutaneous Mastocytosis

Mast cell expansion within the skin has varying degrees of cutaneous involvement. CM can develop as a localized mastocytoma of the skin, maculopapular CM, also known as UP, or the most involved form of diffuse CM. Major and minor criteria to diagnose CM have been proposed. The major criterion is presence of typical skin lesions of mastocytosis associated with the Darier sign.[14] Minor criteria include increased numbers of mast cells in the biopsy of lesional skin and an activating KIT mutation in the lesional skin tissue.[14]