Mastocytosis and Anaphylaxis

Anna Schuch, MD, Knut Brockow, MD*

KEYWORDS

• Mastocytosis • Mast cell activation syndrome • Anaphylaxis • Risk factors
• Triggers • Hymenoptera venom anaphylaxis • Drug-induced anaphylaxis

KEY POINTS

- There are two major forms of indolent systemic mastocytosis associated with anaphylaxis: the classical form with mastocytosis in the skin, and a form without skin lesions becoming apparent only through the occurrence of anaphylactic reactions.
- Anaphylactic reactions in mastocytosis mostly are associated with Hymenoptera stings, but also may be occasionally labeled idiopathic anaphylaxis or triggered by food or drugs.
- In children anaphylaxis is uncommon, mostly idiopathic, and manifests normally during active blistering episodes in those with extensive skin involvement and high serum, whereas adults with systemic mastocytosis carry a 20%–50% risk for anaphylaxis, but with less defined risk factors.
- Because mastocytosis is a well-recognized basis for anaphylaxis, emergency preparedness, including availability and use of emergency medications and, if indicated, life-long venom immunotherapy, is necessary.

INTRODUCTION

Mastocytosis (MC) is a proliferative disorder of hematopoetic mast cell progenitors,[1] which leads to an expansion and accumulation of excessive numbers of mast cells in one or more organs, such as skin, bone marrow, gastrointestinal tract, liver, and spleen.[1,2] The basis of the disease is an activating mutation in the mast cell growth receptor KIT, a protein tyrosine kinase receptor, most commonly a point mutation with exchange of aspartic acid to valine in codon 816 (D816V).[3] More than 80% of all patients with systemic mastocytosis (SM) carry the D816V mutation.[4]

Whereas in most children only the skin seems to be involved (cutaneous MC [CM]), in adults, other organs are also affected (SM). To diagnose SM, according to the World

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Department of Dermatology and Allergy Biederstein, Technische Universität München, Munich, Germany
* Corresponding author. Department of Dermatology and Allergy Biederstein, Technische Universität München, Biedersteiner Straße 29, Munich 80802, Germany.
E-mail address: knut.brockow@tum.de

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Health Organization, several criteria have to be fulfilled. In detail, there are one major and four minor criteria for SM (**Box 1**), of which one major and one minor or three minor criteria are required for diagnosing SM.[2,5]

The overall prevalence of SM in all adults with MC has been reported to be more than 95%.[6,7] In adult SM, there is a subfraction of patients without presence of skin lesions. Comparing these patients with and without MC in the skin (MIS) there is a male predominance and history of insect-sting anaphylaxis in those without MIS.[8] A study, for which patients with classical skin lesions and patients with insect-sting or idiopathic anaphylaxis were recruited, showed almost equal numbers of patients with indolent SM (ISM) with and without skin lesions.[9]

SM is subdivided into different clinical forms according to aggressiveness and prognosis. The most common form (90%–95% of all patients) is ISM. Rare advanced forms are SM with an associated hematologic non–mast cell disorder, aggressive SM and mast cell leukemia.[10] The cumulative probability of disease progression in patients with ISM is low (calculated to be 1.7% in 10 years) and patients with ISM carry a normal life expectancy.[7]

Anaphylaxis is a systemic or generalized life-threatening and potentially fatal systemic hypersensitivity reaction.[11] Clinically, criteria for anaphylaxis have been defined.[12] Typically, it occurs after contact to a known allergen (eg, peanut ingestion) and involves at least two out of the four organ systems: skin (eg, flush, urticaria, angioedema), gastrointestinal tract (eg, abdominal pain, nausea, diarrhea), pulmonary system (eg, wheezing, dyspnea), and cardiovascular system (eg, hypotension, shock).[12]

In addition to patients with SM, there are patients with anaphylaxis that carry clonal mast cells expressing the D816V KIT mutation, but that do not meet enough criteria to diagnose MC. This condition has been named monoclonal mast cell activation syndrome (MMCAS).[13,14]

EPIDEMIOLOGY

Prevalence of Mastocytosis

In 1997 it was calculated that 1 in 1000 to 8000 new patients in dermatology outpatient departments may have some form of MC.[15] More recent studies found a prevalence of ISM of 9.6 to 13 in 100,000 people and an incidence for all subtypes of SM of 0.89 per 100,000 per year.[16,17]

Box 1
Criteria for the diagnosis of systemic mastocytosis

Major criterion

- Multifocal dense aggregates of ≥15 mast cells in bone marrow and/or other extracutaneous tissues

Minor criteria

- Morphologically atypical mast cells in smears of biopsy sections of bone marrow or other extracutaneous organs
- Aberrant expression of CD25 and/or CD2 by mast cells in the bone marrow
- D816V KIT mutation in bone marrow, blood, or other extracutaneous organs
- Serum tryptase levels >20 μg/L