

Original Article

Risk Factor Analysis of Anaphylactic Reactions in Patients With Systemic Mastocytosis

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What is already known about this subject? Anaphylaxis is a common feature in patients with mastocytosis; however, not all patients with mastocytosis experience anaphylaxis. Presently, there are no predictive markers to discriminate patients with mastocytosis at high risk of anaphylaxis from those at low risk.

What does this article add to our knowledge? This is the first study to demonstrate that patients with mastocytosis with anaphylaxis display unique clinical and biological features. A risk analysis model for anaphylaxis was developed and translated into a clinical scoring system.

How does this study impact current management guidelines? The risk assessment tool described here may provide a simple method of identifying and alerting patients with mastocytosis at high risk of anaphylaxis who would benefit from self-injectable epinephrine.

BACKGROUND: Systemic mastocytosis (SM) is a rare disorder of abnormal mast cells in at least 1 extracutaneous organ/tissue. Anaphylaxis is an acute, severe systemic hypersensitivity reaction, and a strong association between SM and anaphylaxis has been shown. However, not all patients with SM experience anaphylaxis. Presently, there are no predictive markers to

discriminate patients with SM at high risk of anaphylaxis from those at low risk.

OBJECTIVE: This study sought to determine risk factors for the occurrence of anaphylaxis in patients with SM.

METHODS: A cross-sectional study was conducted in 122 consecutive adult patients with SM admitted to the Mastocytosis Center at Karolinska University Hospital. All patients underwent medical evaluation, including bone marrow biopsy and a thorough allergy workup. To determine risk factors, study subjects were categorized into 2 groups according to the presence ($n = 55$) or absence ($n = 67$) of anaphylaxis and compared for their demographic, clinical, and biochemical characteristics.

RESULTS: Patients with SM with anaphylaxis had less frequent presence of mastocytosis in the skin ($P < .001$), more atopic predisposition ($P = .021$), higher total IgE levels ($P < .001$), and lower baseline tryptase levels (27 ng/mL vs 42 ng/mL; $P = .024$) compared with patients with SM without anaphylaxis.

CONCLUSIONS: Patients with SM with anaphylaxis display unique clinical and laboratory features. Hence, a risk analysis tool that is capable of discriminating patients with SM at high risk of anaphylaxis from those at low risk with 86% sensitivity was developed by using the variables male sex, absence of mastocytosis in the skin, presence of atopy, IgE levels of 15 kU/L or more, and baseline tryptase levels of less than 40 ng/mL. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Mastocytosis; Anaphylaxis; Risk factors; Tryptase; IgE; Atopy; Venom; Risk assessment tool

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Conflicts of interest: T. Gülen has received research support from Konsul TH C Bergh Foundation and from a regional agreement on medical training and clinical research (ALF) between the Stockholm County Council and the Karolinska Institutet and has received lecture fees from Novartis and ThermoFisher. G. Nilsson has received research support from the Swedish Research Council, from a regional agreement on medical training and clinical research (ALF) between the Stockholm County Council and the Karolinska Institutet, the Swedish Cancer Society, and the Swedish Heart and Lung Foundation. C. Akin has received consultancy fees from Patara Pharma, Deciphera, and Novartis and has a patent for LAD2 cells. C. Ljung declares no relevant conflicts of interest.

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Anaphylaxis is a sudden, severe systemic hypersensitivity reaction resulting from excessive release of mast cell (MC) mediators. Patients can present with a broad array of symptoms and signs, often including skin manifestation, and death may occur because of airway obstruction or cardiovascular collapse.¹

Abbreviations used

ISM- Indolent systemic mastocytosis
MC- Mast cell
MIS- Mastocytosis in the skin
sBT- Serum baseline tryptase
SM- Systemic mastocytosis
VIA- Venom-induced anaphylaxis

Mastocytosis is a heterogeneous disorder characterized by accumulation and activation of clonal MCs in the skin and/or internal organs.^{2,3} In cutaneous mastocytosis, MC accumulation is by definition limited to the skin, whereas in systemic mastocytosis (SM), at least 1 extracutaneous organ/tissue, most often the bone marrow, is involved.³ According to the World Health Organization criteria, patients with SM can be further classified into 4 major subvariants: indolent systemic mastocytosis (ISM), SM with associated clonal hematological non-MC-lineage disease, aggressive SM, and MC leukemia.^{4,5} In adults, the vast majority of patients have ISM.⁶ The clinical manifestations of ISM are protean and range from relatively asymptomatic to frequent episodes of MC mediator symptoms and even life-threatening anaphylaxis.³

The existing evidence indicates a strong association between anaphylaxis and mastocytosis.⁶⁻⁹ The prevalence has been reported to be 20% to 56% in adult patients with various forms of mastocytosis, which represents a 100- to 1000-fold increased risk compared with the general population.¹⁰ The most common elicitors of anaphylaxis in ISM appear to be wasp sting (hymenoptera venom), 53%, followed by reactions without clear trigger, that is, idiopathic, 39%.⁶ Although rare, drugs and food can also be elicitors in patients with SM.^{11,12} The clinical course of anaphylactic reactions in patients with SM is often severe and presents with cardiovascular features including hypotensive syncope.^{6,8,9,13}

Although anaphylaxis is a common feature in patients with SM, some patients with SM never experience anaphylactic episodes and consequently would not need self-injectable adrenaline.

Although the risk of having underlying clonal MC disease, that is, mastocytosis, in patients presenting with anaphylaxis has been studied, there are presently no predictive markers to discriminate patients with SM at high risk of anaphylaxis from those at low risk. This, in turn, creates a challenge for the clinician to make an adequate risk assessment for the patient who has already been diagnosed with SM. Previous observational studies on patients with anaphylaxis and SM suggest that anaphylaxis occurs more often in patients with SM lacking cutaneous engagement^{6,9} and in those with atopic predisposition.^{6,8} A male predominance has also been observed in patients with SM with anaphylaxis.⁸ In contrast, the levels of baseline tryptase have been controversial to assess the risk of anaphylaxis in these patients, and both higher⁹ and lower⁶ tryptase levels have been reported in patients with SM with anaphylaxis compared with those without anaphylaxis.

A risk predicting model that can be used to foresee the occurrence of anaphylaxis in anaphylaxis-naïve patients with SM would therefore be of immense clinical importance. This study sought to validate previously suggested risk factors and to explore new potential ones to predict anaphylaxis in patients with SM. The ultimate aim was to generate a risk predictive model.

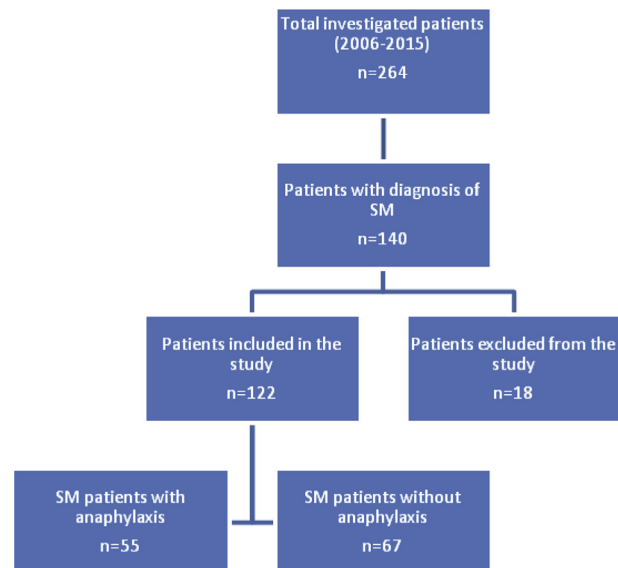


FIGURE 1. Flowchart showing study population and the process of selecting study subjects. Ultimately, study subjects were divided into 2 groups according to presence/absence of anaphylaxis.

METHODS

Study subjects and procedures

The Mastocytosis Center Karolinska was established in 2006 at Karolinska University Hospital and Karolinska Institute in Stockholm, Sweden, and receives referrals from the entire country. As of December 1, 2015, 264 consecutive adult patients (≥ 18 years) had been referred to the center. In accordance with World Health Organization criteria, the diagnostic workup included histopathological evaluation of bone marrow, flow cytometry, *KIT* D816V mutation analysis, and measurement of serum baseline tryptase (sBT) levels. Accordingly, 140 of the investigated patients met the criteria for the diagnosis of SM.

A cross-sectional study was conducted among 122 patients diagnosed with SM after excluding 18 patients with SM because of either inadequate investigation (lack of allergy workup) or lack of consent (Figure 1). Ethical approval was obtained from Regional Ethical Review Board, Stockholm, Sweden (approval no. 2011/1750-31/3). All 122 patients provided their written consent to participate.

All enrolled patients underwent comprehensive allergy workup including detailed medical history and allergy tests at Karolinska University Hospital Huddinge, Department of Respiratory Medicine and Allergy, as previously described.⁶ The clinical relevance of aeroallergens, foods, drugs, and insects was recorded and evaluated by skin prick test and/or specific IgE antibody test (ImmunoCAP Phadiatop, ThermoFisher, Uppsala, Sweden) in relation to patient's medical history. The total IgE level was measured for all patients, always together with the sBT level. The possible effect of general triggers, such as physical exertion, heat, cold, friction, emotional stress, alcohol, or histamine-containing food, was carefully evaluated.

Diagnostic criteria

Diagnosis of SM was made using current World Health Organization criteria, and on the basis of bone marrow investigations to

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