

Recent advances in mast cell clonality and anaphylaxis

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Abstract

Clonal expansion of mast cells carrying the D816V c-kit mutation results in mastocytosis. Recent studies identified the presence of clonal mast cells carrying this mutation in patients with anaphylaxis without classic diagnostic findings of systemic mastocytosis.

Introduction and context

Since the description of the first patient with systemic mastocytosis, the gold standard of diagnosing this disorder has been the demonstration of increased mast cells in clusters in tissue biopsies, most commonly of the bone marrow [1]. Therefore, the term mast cell disease has been used synonymously with mast cell proliferative disorders. Patients with systemic mastocytosis not only have increased mast cells in tissue biopsies but also have elevated serum levels of tryptase (greater than 20 ng/mL), a mast cell protease used as a surrogate marker of mast cell burden (Table 1). Molecular mechanisms resulting in the accumulation of mast cells in mastocytosis have not been completely elucidated; however, a gain-of-function mutation in c-kit (D816V) is found in almost all patients with systemic mastocytosis [2]. This mutation renders the Kit tyrosine kinase independent of its ligand stem cell factor, resulting in constitutive autophosphorylation and activation of downstream signal transduction cascades. Kit is expressed in large quantities on mast cell membrane and functions to induce differentiation and proliferation of mast cell progenitors, protect them from apoptosis, and enhance mast cell activation [3].

Recent advances

Patients with mastocytosis are at higher risk for developing hypotensive episodes resembling anaphylaxis [4]. A recent study estimated the incidence of anaphylaxis

to be as high as 49% in patients with mastocytosis, representing approximately a 1000-fold increase in incidence compared with the general population [5]. The most common etiologic factors of anaphylaxis are drugs, foods, exercise, and Hymenoptera stings. However, an etiology cannot be identified in a significant proportion of patients referred to allergists after one or more episodes of anaphylaxis [6]. These patients are termed to have idiopathic anaphylaxis. Based on the observation that mast cell disease is associated with increased risk of anaphylaxis, patients with unexplained anaphylaxis have been studied for the presence of aberrant clonal bone marrow mast cells as seen in mastocytosis. One study found that 5 out of 12 patients with recurrent anaphylaxis had aberrant mast cells as identified by such markers as the c-kit D816V mutation or the expression of CD25 surface marker [7]. Interestingly, these patients did not have any apparent diagnostic evidence of a proliferative mast cell disease such as clusters of mast cells in bone marrow or urticaria pigmentosa skin lesions. The demonstration of aberrant mast cells in these patients required sensitive techniques of flow cytometry or mutation analysis of enriched mast cells. Thus, these patients presented with a disorder characterized primarily by activation rather than proliferation of mast cells, despite carrying the same c-kit mutation in systemic mastocytosis. Such patients who lack major diagnostic criteria of mastocytosis (multifocal aggregates of mast cells in tissue biopsies) but who are detected to have

Table 1. Diagnostic criteria for systemic mastocytosis

Major
Multifocal clusters of 15 or more mast cells in a biopsy of tissue such as bone marrow
Minor
1. Serum baseline tryptase of greater than 20 ng/mL
2. Aberrant expression of CD25 or CD2 or both on mast cells
3. Presence of a codon 816 mutation (most commonly D816V) in peripheral blood or a lesional tissue
4. Morphologic abnormalities of bone marrow mast cells (spindle shapes, hypogranulation, or bilobated or multilobated nuclei)

Either one major and one minor or three minor criteria are needed to make a diagnosis of systemic mastocytosis.

one or two minor diagnostic criteria (c-kit mutation, CD25 expression, or morphologic abnormalities such as spindle shapes and hypogranulation) are termed to have 'monoclonal mast cell activation syndrome' (MMAS) [8,9]. Some patients with MMAS have normal or only slightly elevated serum tryptase levels, making it especially challenging to diagnose a mast cell disorder. From the hematopoietic clonal standpoint, this nomenclature is perhaps analogous to monoclonal gammopathy of undetermined significance, which represents a plasma cell disorder with a limited clonal expansion. Follow-up of these patients so far has suggested that most do not progress to systemic mastocytosis (personal observation).

Recent studies examined the role of mast cell clonality in patients who experience anaphylaxis after Hymenoptera stings [10]. In a study examining 379 patients with systemic reactions to Hymenoptera stings, it was found that approximately 12% have elevated baseline tryptase levels [11]. Approximately 62% of these patients with elevated tryptase levels satisfied the criteria for systemic mastocytosis, whereas 26.5% had MMAS. The incidence of clonal mast cell disease in patients who experience anaphylaxis to other triggers such as drugs and foods has also been investigated and found to be approximately 1.5%, while 6.6% of this population had elevated tryptase levels [12]. Clinical analysis of symptomatic presentation of patients with clonal mast cell disease showed that they suffered significantly more hypotensive episodes in the absence of urticaria as compared with patients with true idiopathic anaphylaxis [13].

Implications for clinical practice

Based on these recent findings, we recommend the investigation of occult or overt mast cell disease in all patients with recurrent hypotensive anaphylaxis episodes, especially those with idiopathic anaphylaxis and Hymenoptera sensitivity. A baseline tryptase level should be obtained at a minimum in addition to the usual workup to determine an allergic etiology. Patients with elevated baseline tryptase levels should

be referred to a specialized center to have clonal mast cell disease investigated.

Clinical management of patients with clonal mast cell disease includes symptomatic therapy with antimediation medications such as antihistamines, antileukotriene medications, glucocorticoids, and cromolyn individualized for each patient. Self-injectable epinephrine should be considered for every patient due to the increased risk of anaphylaxis. Patients with a history of Hymenoptera anaphylaxis should be referred to an allergist for evaluation of IgE-mediated sensitization. If found to have allergic Hymenoptera sensitization, patients with clonal mast cell disease are candidates for lifelong Hymenoptera venom immunotherapy.

Abbreviation

MMAS, monoclonal mast cell activation syndrome.

Competing interests

The author declares that he has no competing interests.

References

1. Metcalfe DD: **Mast cells and mastocytosis.** *Blood* 2008, **112**:946-56.
2. Akin C: **Molecular diagnosis of mast cell disorders: a paper from the 2005 William Beaumont Hospital Symposium on Molecular Pathology.** *J Mol Diagn* 2006, **8**:412-9.
3. Jensen BM, Akin C, Gilfillan AM: **Pharmacological targeting of the KIT growth factor receptor: a therapeutic consideration for mast cell disorders.** *Br J Pharmacol* 2008, **154**:1572-82.
4. Muller UR, Haerberli G: **The problem of anaphylaxis and mastocytosis.** *Curr Allergy Asthma Rep* 2009, **9**:64-70.
5. Brockow K, Jofer C, Behrendt H, Ring J: **Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients.** *Allergy* 2008, **63**:226-32.
6. Webb LM, Lieberman P: **Anaphylaxis: a review of 601 cases.** *Ann Allergy Asthma Immunol* 2006, **97**:39-43.
7. Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, Metcalfe DD: **Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with 'idiopathic' anaphylaxis.** *Blood* 2007, **110**:2331-3.
8. Sonneck K, Florian S, Müllauer L, Wimazal F, Födinger M, Sperr WR, Valent P: **Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: monoclonal mast cell activation syndrome.** *Int Arch Allergy Immunol* 2007, **142**:158-64.

9. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, Castells M, Sperr WR, Kluin-Nelemans HC, Hamdy NA, Lortholary O, Robyn J, van Doormaal J, Sotlar K, Hauswirth AW, Arock M, Hermine O, Hellmann A, Triggiani M, Niedoszytko M, Schwartz LB, Orfao A, Horny HP, Metcalfe DD: **Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations, and response criteria.** *Eur J Clin Invest* 2007, **37**:435-53.
10. Rueff F, Placzek M, Przybilla B: **Mastocytosis and Hymenoptera venom allergy.** *Curr Opin Allergy Clin Immunol* 2006, **6**:284-8.
11. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, Castellani L, Bonetto C, Frattini F, Dama A, Martinelli G, Chilosi M, Senna G, Pizzolo G, Zanotti R: **Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels.** *J Allergy Clin Immunol* 2009, **123**:680-6.
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12. Bonadonna P, Zanotti R, Pagani M, Caruso B, Perbellini O, Colarossi S, Olivieri E, Dama A, Schiappoli M, Senna G, Antico A, Passalacqua G: **How much specific is the association between Hymenoptera venom allergy and mastocytosis?** *Allergy* 2009, **64**:1379-82.
13. Koterba A, Akin C: **Differences in the clinical presentation of anaphylaxis in patients with indolent systemic mastocytosis (ISM) versus idiopathic anaphylaxis (IA).** *J Allergy Clin Immunol* 2008, **121**(Suppl 1):S68-9.