Published in final edited form as:
J Allergy Clin Immunol. 2009 March ; 123(3): 687–688. doi:10.1016/j.jaci.2009.02.003.

Assessing anaphylactic risk? Consider mast cell clonality

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Keywords

anaphylaxis; tryptase; mast cells; KIT; venom

The ability to predict risk for severe anaphylaxis is an important goal for physicians. Bonadonna et al advance this effort with data from a 3-year prospective study that analyzed 44 patients with a serum baseline total tryptase (sBT) level >11.4 ng/ml who were culled from 379 patients with a prior systemic immediate hypersensitivity reaction to a hymenoptera sting.(1) Their data indicate that the majority of such patients have an underlying clonal mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome,(2) by assessing the bone marrow for mast cell granulomas, spindle-shaped mast cells and mast cells expressing surface CD2 or CD25; and the serum for an elevated sBT level. This is the most comprehensive study to date of the relationship between hymenoptera sting-induced anaphylaxis, sBT levels and mast cell clonality. The article raises important issues relating to sBT levels; and activating mutations in KIT (which appear to result in a hyper-responsive mast cell phenotype) as biomarkers for anaphylactic risk.

sBT levels elevated in the setting of a hypotensive or systemic immediate hypersensitivity event, i.e. “anaphylaxis”, have been used as evidence of mast cell degranulation. Persistent elevation in sBT >20 ng/ml has been set as a minor diagnostic criterion for the diagnosis of mastocytosis. Importantly, in this study by Bonadonna et al, a sBT level of >11.4 ng/ml not only identified patients likely to have a clonal mast cell disorder, but also those at risk for systemic anaphylaxis. In fact, an odds ratio of 6.2 (95% confidence interval 3.1-12.4) can be calculated for having had a stage IV anaphylactic reaction if the sBT level was >11.4 ng/ml among the patient group with a systemic reaction to a hymenoptera sting. A heightened risk for more severe anaphylactic reactions to hymenoptera stings in those with an elevated sBT has been noted previously. (3-5) An analogous odds ratio calculation for risk of mast cell clonality in subjects with elevated sBT levels cannot be made in the current study, because clonality was not assessed in the 335 subjects with normal sBT levels.

Elevated sBT levels in patients diagnosed with systemic mastocytosis were first reported in 1995 (6), where 29 of 46 patients with indolent mastocytosis had levels >20 ng/ml. Among patients with urticaria pigmentosa, but without histologic evidence for systemic mastocytosis

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Disclosure of potential conflict of interest: Virginia Commonwealth University receives royalties from Phadia for licensing rights to the tryptase assay, and shares those royalties with L.B. Schwartz, the inventor.

on the bone marrow biopsy, 3 of 13 had a baseline sBT level >20 ng/ml; the remaining 10 had sBT levels <11.4 ng/ml. Among those with a positive bone marrow biopsy for systemic mastocytosis by histology, 32 of 33 had sBT levels >11.4 and 26 of 33 had sBT levels >20 ng/ml. Thus, even in this early study that predated more sensitive markers of mastocytosis, such as expression of surface CD25 or CD2 on mast cells, and of activating KIT mutations, it was apparent that as many as 20% of the cases of systemic mastocytosis might be missed with a threshold sBT of 20 ng/ml. Thus, the current WHO criterion of a sBT level of >20 ng/ml as one of the minor diagnostic markers for mastocytosis(7) may need to be lowered, at least in patients with a history of a systemic immediate hypersensitivity reaction to a hymenoptera sting. This lower sBT level would apply to those with or without evidence for IgE reactivity to venom, because each of the four patients without IgE sensitization in the current study had elevated baseline sBT levels along with bone marrow evidence for mast cell clonality. It remains to be determined whether the sBT threshold at which an underlying/mast cell clonality disorder is suspected should be lowered in subjects who have had provoked or unprovoked anaphylaxis. Previously, 2 of 56 healthy controls had sBT levels between 11.4 and 20 ng/ml. (6) Consequently, a sBT threshold of <20 ng/ml might falsely identify healthy individuals as having/mastocytosis. Nevertheless, a bone marrow biopsy to assess mast cell clonality is reasonable to consider in a patient with anaphylaxis to insect stings and an elevated sBT above 11.4 ng/ml, though confirmatory clinical studies should be performed before this practice comes under consideration as a standard of care.

Based on the observations that α/β-protryptases are spontaneously secreted by unstimulated mast cells in culture,(8) and appear to be the principal form of tryptase detected in serum or plasma in both healthy patients and those with systemic mastocytosis when their clinical signs and symptoms are quiescent, levels of these tryptase precursors appear to correspond to the total body burden of mast cells.(9) Theoretically, other factors may affect the sBT level by influencing the amount of protryptases secreted per cell. For example, perhaps having KIT in a chronically activated state might affect the amount of these precursors being secreted by otherwise unstimulated mast cells. In addition to systemic mastocytosis, elevated sBT levels have been observed in acute myelocytic leukemia, end stage renal disease, refractory anemias, myelodysplastic syndromes, hypereosinophilic syndrome associated with the FIP1L1-PDGFRA fusion mutation and during rhSCF administration.

Mutations in KIT at codon 816 were first associated with systemic mastocytosis in 1995,(10) and subsequently became a minor diagnostic criterion for the diagnosis of mastocytosis.(7) The most common mutation at codon 816 is D816V, which is an “activating” mutation that results in ligand independent autophosphorylation, the initiation of downstream signaling events, the proliferation of mast cell precursors and enhanced survival of mature mast cells. Laboratory experiments revealed that this mutation also enhances mast cell degranulation initiated following FcεRI aggregation. The ability of KIT to enhance FcεRI-dependent mast cell degranulation occurs through phosphorylation of a common adaptor molecule, NTAL (LAT2).(11)

The association of codon 816 mutations in KIT with hyper-responsiveness of human mast cells became of interest following reports that spontaneous anaphylaxis within the mastocytosis population occurred with a cumulative frequency substantially more than that observed in the general population.(12;13) Together, these observations raised the possibility that an activating/mutation resulted in a hyper-responsive phenotype. This possibility was supported by a recent report that among patients with idiopathic anaphylaxis, some harbor an activating codon 816 mutation in KIT within the mast cell population.(2) These observations and others led to the concept of a “monoclonal mast cell activation syndrome” where abnormal mast cells are believed to arise from a single pluripotential cell. This syndrome was defined at a recent consensus conference as one which occurs in patients who exhibit spontaneous anaphylaxis

and manifest at least two minor criteria of mastocytosis in the absence of cutaneous disease. (14) This monoclonal mast cell activation syndrome was identified by Bonadonna et al in 9 of the 34 patients with elevated tryptase who had agreed to a bone marrow examination.

These events in turn raise several intriguing questions. First, could activating/mutations in KIT exacerbate IgE-mediated allergic inflammation that in turn lowers the stimulus threshold for anaphylaxis? For example, in mice, IL-4 and possibly IL-13 increase the responsiveness of blood vessels to mast cell vasoactive mediators.(15) Second, could it be that other mutations and polymorphisms within the mast cell signalosome similarly result in a mast cell hyper-responsive phenotype? This latter idea appears to be substantiated by a report that mast cells cultured from CD34-positive cells from patients with chronic idiopathic urticaria have an increase in spontaneous histamine release after IgE sensitization, and that this correlated with increased expression of Syk.(16) The paper by Bonadonna et al did identify activating/ mutations in KIT within the population selected for bone marrow biopsy; however, it is possible that some patients with KIT mutations were in the group with tryptase values below 11.4 ng/ ml, and that other hyper-responsive mast cell phenotypes may exist that either complement activating KIT mutations or act independently of KIT. Further research is needed to determine if mast cell responsiveness is one determinant of the threshold to elicit an allergic reaction and perhaps the subsequent severity of the allergic inflammatory response.(17) A corollary to this line of thought is that inhibiting the tyrosine kinase activity of activating/mutations in KIT might not only decrease the mast cell burden, but also diminish mast cell reactivity.(18) In addition, other interventions to reduce anaphylactic risk in patients with an sBT>11.5 ng/ml and a history of a systemic insect sting reaction should be considered and explored through clinical trials. Such approaches might include the use of omalizumab (19) or venom immunotherapy. (20)

Acknowledgments

This work was partially supported by the Division of Intramural Research, NIAID, NIH

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