

Angioedema and High Tryptase: To Marrow or Not to Marrow?

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A “Practice Pearl” helps an allergist-immunologist practice more safely, effectively, timely, efficiently, equitably, or in a more patient-centered way. This feature is coordinated by Stuart Abramson, MD, Giselle Mosnaim, MD, and Andrew Murphy, MD, from the AAAAI Federation of Regional, State, and Local Allergy, Asthma, and Immunology Societies Assembly and by Editorial Board member Matthew Rank, MD. More information about submitting a “Practice Pearl” can be found on our Web site (jaci-inpractice.org).

PRACTICE CHALLENGE

A 66-year-old Caucasian man was found to have persistently elevated serum tryptase (28–38 ng/mL) after an acute episode of facial swelling and flushing initially attributed to angiotensin converting enzyme (ACE) inhibitors (ACEI). After ACEI discontinuation, evaluation for causes of angioedema and flushing—including hereditary angioedema, insect allergies, and pheochromocytoma—yielded negative results. Workup for an underlying mast cell disorder likewise did not identify the p.D816V *KIT* missense or the *FIPL1-PDGFR* gene fusion. *N*-Methylhistamine in urine and soluble CD25 were not elevated. The patient remained asymptomatic on H1 and LTR antagonists after his initial episode and denied other symptoms of mast cell activation. This case raised challenging questions. Is a bone marrow (BM) biopsy warranted or even justified? Can we rely on symptoms and elevated tryptase alone to make this decision?

PRACTICE SOLUTION

Genetic analysis for hereditary alpha tryptasemia (HaT) should be considered when determining whether to perform a BM biopsy. This assay is now offered as a commercially available Clinical Laboratory Improvement Amendments (CLIA)-approved genetic test. HaT is an autosomal dominant genetic trait caused by increased alpha-tryptase encoding *TPSAB1* copy

number. Affected individuals have elevated basal serum tryptase (BST) levels ≥ 8 ng/mL; levels resulting from triplications are 24 ± 6 ng/mL.¹ Our patient had a *TPSAB1* triplication. The HaT prevalence may exceed 5% in some populations; however, some individuals report few symptoms. Aside from his acute episode, our patient has been largely asymptomatic. The clinical significance of this structural genetic variant in asymptomatic individuals is yet to be determined. Furthermore, the diagnosis of HaT does not preclude the presence of clonal mast cell disease.²

Weighed risks and benefits of BM aspiration and biopsy were carefully considered in our patient. Urticaria and angioedema are uncommon as the heralding findings of clonal mast cell disease, and our patient did not have hypotensive syncope, which may have justified a more aggressive workup. Given that HaT explained the elevated serum tryptase level, and the lack of additional or recurrent symptoms, a BM biopsy was not performed.

The final diagnosis in this patient was ACEI-related angioedema; we cannot know whether HaT may have modified his risk or presentation. However, this case highlights the need for additional clinical criteria that identify patients who will benefit from BM biopsy. The utility of serum tryptase as a biomarker for mast cell activation must also be questioned in the context of this patient, and potentially others with elevated BST. Basal levels varied by 10 ng/mL—a level much greater than the consensus diagnostic cutoff of $20\% + 2$ ng/mL. This cutoff has been validated during symptomatic events caused by mast cell mediator release in patients without elevated BST. However, in our patient, these levels were obtained while he was asymptomatic and the high degree of variance would confound the interpretation of a level obtained during an acute symptomatic episode. We will continue to monitor annually for signs of hematologic dyscrasia by physical examination and complete blood count (CBC) with differential, as well as by obtaining annual BST and total IgE with upward or downward trends, respectively, suggesting potential clonal disease. However, this case and approach highlight the critical need for additional validated objective measures to guide medical decision making in patients with suspected mast cell–related disease.

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