Nonhistaminergic Idiopathic Angioedema May Be a Presentation of Mast Cell Activation Syndrome

LB Afrin
Division of Hematology/Oncology, Medical University of South Carolina, Charleston, South Carolina, United States of America

Key words: Angioedema. Mast cell activation syndrome. Icatibant.

Palabras clave: Angioedema. Síndrome de activación mastocitaria. Icatibant.

In their intriguing case report, Colás et al [1] presented a patient with recurrent nonhistaminergic idiopathic angioedema (NHIA) who was unresponsive to antihistamines and corticosteroids. There was no evidence of C1 esterase inhibitor deficiency or factor XII mutations, and serum tryptase was normal. Subsequent treatment with icatibant proved effective. The mechanistic origin of the angioedema was unclear.

Recently, mast cell heparin (MCH) was found to initiate formation of bradykinin (BK) in a factor XII–dependent manner [2,3]. MCH activates factor XII, and activated factor XII activates prekallikrein (PK). Activated PK cleaves BK from high-molecular-weight kininogen. Freed BK binds to B2-kinin receptor, increasing vascular permeability and dilation that in turn leads to edema and even hypotension [2,4].

Since the first published description in 2007 of mast cell activation syndrome (MCAS) [5], there has been rapid development of new understanding that mastocytosis (systemic and otherwise) is but the proliferative tip of the iceberg of mast cell activation disease, while the relatively nonproliferative body of the iceberg, hidden below the waterline of clinical recognizability, is the large menagerie of diseases of constitutive mast cell activation now collectively known as MCAS [6,7]. While a few (rare) mutations, largely in specific strategic sites in the dominant mast cell regulatory element KIT, seem to drive most cases of (rare) mastocytosis and its clinical features, a menagerie of other mutations in mast cell KIT have been found in patients with MCAS [8]. These mutations likely drive assorted patterns of (dysregulated) mediator production and release, with little cell accumulation or proliferation, to produce the clinical presentations of MCAS, which are extremely heterogeneous but commonly include angioedematous features. The serum tryptase level is now understood to reflect total body mast cell load far more than mast cell activation state, and while the tryptase level is very often significantly elevated in (proliferative) mastocytosis, it is almost always barely or not elevated in MCAS [7].

Given that heparin is a major product of mast cells and that mast cells are typically found not only at environmental interfaces but also at perivascular sites, it is possible that MCAS underlies at least some cases of NHIA via the MCH-BK pathway. Given its mutational and thus clinical heterogeneity, it is no surprise that MCAS also exhibits considerable heterogeneity of therapeutic responsiveness, and while most MCAS patients eventually identify a helpful regimen of agents targeted at controlling mast cells or blocking their released mediators, symptoms—including angioedema—persist in some cases despite trials with several therapies. Icatibant has not yet been studied in MCAS but, at least from a mechanistic perspective, it may hold promise for MCAS patients plagued by NHIA and presyncope/syncope.

References

1. Colás C, Montoiro R, Fraj J, Garcés M, Cubero JL, Caballero T. Nonhistaminergic idiopathic angioedema: clinical response to icatibant. J Investig Allergol Clin Immunol. 2012;22(7):520-31.
2. Oschatz C, Maas C, Lecher B, Jansen T, Björkqvist J, Tradler T, Sedlmeier R, Burfeind P, Cichon S, Hammerschmidt S, Müller-Esterl W, Willemin WA, Nilsson G, Renné T. Mast cells increase vascular permeability by heparin-initiated bradykinin formation in vivo. Immunity. 2011;34(2):258-68.
3. Renné T, Schmaier AH, Nickel KF, Blombäck M, Maas C. In vivo roles of factor XII. Blood. 2012;120(22):4296-303.
4. Siebeck M, Cheronis JC, Fink E, Kohl J, Spies B, Spannagl M, Jochum M, Fritz H. Dextran sulfate activates contact system and mediates arterial hypotension via B2 kinin receptors. J Appl Physiol. 1994;77(6):2675-80.
5. Sonneck K, Florian S, Mullauer L, Wimazal F, Fodinger 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(2):158-64.
6. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic Criteria. J Allergy Clin Immunol. 2010;126:1099-104e4.
7. Molderings GJ, Brettner S, Homann J, Afrin LB. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol. 2011;4:10-7.
8. Molderings GJ, Meis K, Kolck UW, Homann J, Frieling T. Comparative analysis of mutation of tyrosine kinase Kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. Immunogenetics. 2010;62:721-7.