Review Article

Expanding Spectrum of Mast Cell Activation Disorders: Monoclonal and Idiopathic Mast Cell Activation Syndromes

Matthieu Picard, MD; Pedro Giavina-Bianchi, MD, PhD; Veronica Mezzano, MD; and Mariana Castells, MD, PhD

Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

ABSTRACT

Background: In recent years, 2 new syndromes of mast cell activation have been described in patients with episodes of mast cell mediator release that range from flushing and abdominal cramping to anaphylaxis: monoclonal mast cell activation syndrome (MMAS) and idiopathic mast cell activation syndrome (MCAS).

Objective: This review will discuss these 2 new syndromes in the larger context of mast cell activation disorders as well as the diagnostic and treatment approaches for these conditions.

Methods: PubMed was searched using the following terms: *mast cell activation disorder*, *mast cell activation syndrome*, and *clonal mast cell*. Only English-language articles published up until February 27, 2013, were considered.

Results: MMAS has been diagnosed in patients with systemic reactions to hymenoptera stings and elevated baseline serum tryptase as well as in patients with unexplained episodes of anaphylaxis. A bone marrow biopsy establishes the diagnosis by revealing the presence of monoclonal mast cells that carry the D816V *KIT* mutation and/or express CD25 while the diagnostic requirements for systemic mastocytosis are not met. MCAS affects predominantly women in whom no mast cell abnormality or external triggers account for their episodes of mast cell activation. MCAS is a diagnosis of exclusion, and primary and secondary mast cell activation disorders as well as idiopathic anaphylaxis have to be ruled out before making the diagnosis. Patients with MCAS and MMAS are treated in a stepwise fashion with drugs that block the effects of mediators released by mast cells on activation. One third of MCAS patients experience complete resolution of symptoms with treatment, while one third have a major response and one third a minor response to treatment. A combination of drugs is usually necessary to achieve symptom control. No drug trial has been performed in patients with MMAS and MCAS.

Conclusions: MMAS and MCAS are 2 newly described, rare syndromes of mast cell activation. Further studies will be necessary to better understand the cause of these conditions and their natural evolution and to validate and improve the treatment approach. Research should also focus on developing drugs with the potential to cure these debilitating disorders. To achieve these goals, centers with expertise in mast cell activation disorders are essential as they allow for a critical mass of these patients to be enrolled in studies while providing those patients with the most up-to-date diagnostic procedures and treatment strategies. (*Clin Ther*. 2013;35:548–562)

Key words: antihistamine, mast cell activation syndrome, mastocytosis, monoclonal, treatment.

INTRODUCTION

Anaphylaxis is the most dramatic clinical reaction mediated by mast cells. It is characterized by the sudden onset of skin, cardiovascular, respiratory, gastrointestinal (GI), and neuromuscular symptoms and can rapidly lead to death.[1] Although it is widely known that mast cells are activated in the context of an allergic reaction by the allergen-induced cross-linking of surface immunoglobulin (Ig) E/FcεRI (the high-affinity receptor for the Fc region of IgE), it should be rec-

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ognized that many other stimuli and conditions can cause mast cell activation and therefore lead to anaphylaxis.[2] In this regard, 2 *new* syndromes pertaining to mast cell activation have recently been described and deserve special attention: monoclonal and idiopathic mast cell activation syndrome, abbreviated respectively as MMAS and MCAS.

From a clinical standpoint, MMAS and MCAS share many similarities with systemic mastocytosis (SM), a primary disorder of mast cells in which patients experience symptoms ranging from pruritus and flushing to anaphylaxis.[2] SM is caused in >90% of patients by the D816V *c-KIT* gain-of-function somatic mutation.[3,4] The *c-KIT* gene codes for the transmembrane receptor KIT, which transmits signal on engaging its ligand, stem cell factor, and affects growth, differentiation, apoptosis, and activation of mast cells.[5] Therefore, in patients with SM, mast cells are found to be morphologically and functionally abnormal and increased in numbers through clonal expansion.[3] Recently, several groups identified patients with either "idiopathic anaphylaxis" (IA) or systemic reactions to hymenoptera stings in whom mast cells showed clonal abnormalities, alike those seen in SM, but that failed to meet its diagnostic requirements.[6–10] The denomination of MMAS was chosen to characterize this syndrome, which importantly does not appear to simply be an early form of SM.[3,4] In another category of patients with evidence of episodic mast cell activation, investigators have failed to find any mast cell abnormality or external triggers that could explain those episodes.[8,9,11] In 2010, Akin et al[4] proposed diagnostic criteria for this syndrome, which was named *MCAS*. It requires objective evidence of mast cell activation and exclusion of any other known mast cell activation disorder.[4] Its diagnostic criteria have recently been endorsed by an international consensus.[2] This review will discuss these 2 new syndromes, MMAS and MCAS, in the larger context of mast cell activation disorders as well as the diagnostic and treatment approaches for these disorders.

MATERIALS AND METHODS

PubMed was searched using the following terms: *mast cell activation disorder, mast cell activation syndrome,* and *clonal mast cell*. Only English-language articles published up until February 27, 2013, were considered.

RESULTS

Three retrospective cohort studies provided clinical and laboratory data on patients with MCAS, and 1 gave information on their responses to treatment.[8,9,11] Patients with MMAS were described in 5 retrospective studies, which mainly detailed their laboratory features, and none provided data on treatment.[6–10]

Mast Cell Activation Disorders: Diagnostic Criteria and Differential Diagnosis

The clinical features of mast cell activation disorders result from the actions of the various mediators released by mast cells following their activation (**Table I**).[2,12–15] However, none of these are specific for mast cell activation, and many other conditions need to be considered in the differential diagnosis. Therefore, a comprehensive clinical history, physical examination, and basic laboratory tests are crucial in the patient evaluation. Some rather rare diseases and some more common ones deserve special consideration (**Table II**).[16]

Many diseases can cause flushing, which is very common in patients with mast cell activation disorders, and, although accompanying signs and symptoms are helpful in excluding some of them, it is often necessary to order additional tests.[17] Carcinoid tumors release many mediators in an episodic fashion, some of them being also released by mast cells on activation (eg, histamine [H], prostaglandins).[18] This partly explains their similar clinical features (flushing, bronchospasm, diarrhea, hypotension) and that they can both respond to antihistamines.[19] This diagnosis can usually be excluded based on a normal 24-hour urine 5-hydroxyindoleacetic acid level.[18] Whereas the classic triad of headache, sweating, and tachycardia with hypertension readily orients toward a diagnosis of pheochromocytoma, most patients with this condition present with an incomplete triad and with symptoms suggestive of mast cell activation.[20] Measurement of 24-hour urine fractionated metanephrines and catecholamines is a highly sensitive and specific diagnostic test for this disorder.[21] Medullary cancer of the thyroid can cause flushing and diarrhea in patients with advanced disease, at which time they usually also show signs and symptoms of local involvement and have an increased serum calcitonin level.[22]

Patients with postural tachycardia syndrome are frequently young women who experience many symptoms reminiscent of mast cell activation (lightheadedness, fatigue, anxiety, dyspnea, palpitations, and even syncope) on standing.[23] Moreover, superimposed mast