Theme Editorial

The Many Faces of Mast Cell Disorders—A House of Mirrors?

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Normal mast cells are complex enough. We see deeper into their mystery every year as we probe their receptor-mediated interactions, their intracellular signaling pathways, and a multitude of their products that mediate a wide range of allergic and other conditions.[1] But abnormal mast cells are even more insidious. Patients with mast cell disorders generally present either with anaphylaxis or with less severe and less specific symptoms that often lead to delayed diagnosis or misdiagnosis. Mast cell disorders have become an increasing focus of our clinical practice due, in part, to the growing popularity of mast cell activation syndrome (MCAS) as an internet diagnosis for whatever ails you. In the past, a practicing allergist might have safely assumed that they would never see a case of mastocytosis in their career. Now, one must be able to separate the wheat from the chaff. Mast cell disorders can be even more challenging to rule out than to confirm and our ultimate diagnostic test, bone marrow biopsy, is often difficult for patients to accept. So what is an allergist-immunologist to do? The authors in this issue provide an excellent framework for the clinical assessment, diagnostic evaluation, and therapeutic decision making in patients with suspected or proven mast cell disorders.

Mastocytosis is defined by international criteria, but we have become increasingly aware that there is some overlap of mastocytosis (a primary mast cell activation disorder) with other conditions that involve mast cell activation (secondary and idiopathic mast cell activation disorders).[2] In patients presenting with anaphylaxis of unknown cause, the question has grown from "Is it idiopathic anaphylaxis (IA) or mastocytosis?" to "Is it something else?" Studies in the past few years have examined the overlap of mast cell disorders including IA, alpha-gal syndrome, insect sting anaphylaxis, MCAS, and alpha-tryptasemia.[3-7] We have also seen the changing epidemiology of anaphylaxis in many areas. In a recent study in an endemic area, alpha gal (19%) was one of the most common causes of anaphylaxis, although IA (35%) was the most common cause in that study of 218 cases.[8] Several of the authors in this issue bring to the readers' attention the recent reports of a new confounder in the evaluation of mast cell disorders. Alpha-tryptasemia is a genetic trait associated with increased numbers of copies of the alpha tryptase gene, and therefore increased production of tryptase, which may account for most of the cases of elevated basal serum tryptase in the general population.[5] The clinical significance of this finding and the potential role in the spectrum of mast cell disorders is not yet known.

The likelihood of clonal mast cell disease may depend on the population studied, and how the patient presents clinically. This is evident in a most unusual case presented by Golden and Carter,[9] in which there were ultimately 4 diagnoses, including the presenting sign of insect sting anaphylaxis, as well as IA, mastocytosis, and alpha-gal anaphylaxis.[9] The clinical presentation may indicate the likelihood of other concomitant mast cell conditions. Carter et al[3] found that venom was not a predictor of mastocytosis in patients who present with IA, but venom is a major predictor of mastocytosis in patients who present with sting anaphylaxis.[7] In this issue, Kulinski et al[10] also describe the potential overlap of exercise-induced anaphylaxis with mastocystosis. The diagram in Figure 1 depicts some of the major conditions discussed in this issue and the fact that there is significant overlap in these conditions. The extent of this overlap is not yet fully understood, and the relative sizes of the circles in this diagram are not drawn to any exact proportion. However, it is becoming increasingly clear that patients who present with any one of these conditions warrant a complete history and physical including consideration of other forms of mast cell disorders.

The concept of MCAS arose to describe patients with symptoms and signs consistent with mast cell mediator release, who had laboratory-confirmed increase in tryptase and/or other mediators, and significant clinical improvement in response to mast cell mediator blockade. Expert panel reports described proposed criteria and the most likely symptoms, signs, and mediators to be found in MCAS.[6] However, the symptoms can be quite nonspecific, contributing to the use of MCAS as a diagnostic catch-all for almost any unexplained symptoms. Indeed, as allergists, we may find ourselves "delabeling" patients more often than confirming the diagnosis.

The difficulty in defining MCAS for the practicing clinician is evident in many of the articles in this issue. The review article by Valent and Akin[11] describes the importance of adhering to the established criteria. They describe the established criteria including "the episodic (recurrent) occurrence of systemic symptoms that are produced by mast cell mediators and involve at least two organ systems." However, the authors go on to state that "Most MCAS patients suffer from recurrent episodes of severe hypotension (anaphylaxis)." This definition of MCAS is similar to that of recurrent IA (with elevated tryptase during the episodes). In a recent review, there is a figure that depicts IA as

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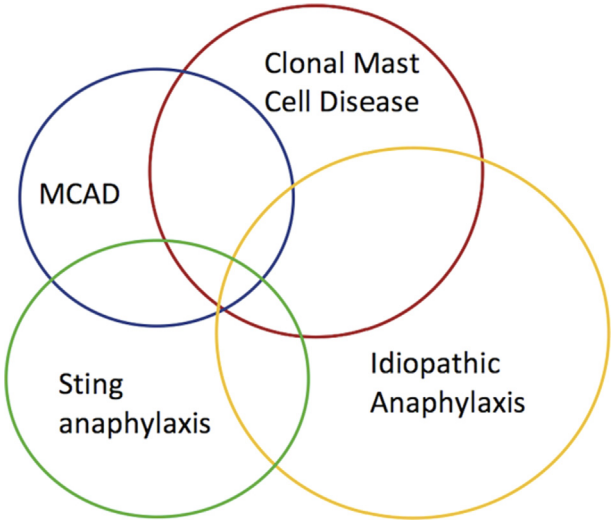

FIGURE 1. Diagrammatic representation of possible overlap of multiple mast cell–related disorders. *MCA*D, Other mast cell–related disorders such as alpha-gal syndrome, alpha-tryptasemia, and nonclonal MCAS. (Note that figure elements are not necessarily in correct proportion.)

being a small subset of MCAS, whereas the proposed change to the criteria seems to make MCAS a subset of IA.[12] Or are they one and the same?

Another difference in this review is the focus on tryptase to the exclusion of other mast cell mediators. Other mediators may derive from different cell types, and the change from baseline that would indicate a significant increase during a reaction has not been defined for other mediators. Increases in other mediators could indeed be associated with symptoms of MCAS, but might not necessarily be caused by MCAS. This begs the question of what might cause typical symptoms with a clear increase in plasma histamine or blood prostaglandin D2, but no increased tryptase. Could there be a basophil activation syndrome?

These proposed criteria for the diagnosis of MCAS are, in part, a response to the large numbers of patients who present with a "diagnosis" of MCAS made by internet searches, friends, relatives, and physicians. This was recently expressed by the same authors as a "call for research."[13] There is clearly a need for prospective studies to characterize the spectrum of MCAS that might fall within the previous consensus criteria. Although our understanding of MCAS is incomplete, the authors correctly emphasize the need to adhere to consensus criteria and discourage any broader definition leading to inappropriate diagnosis. The diagnostic approach to patients with suspected mast cell disorders is also clearly set out in the review by Greenberger and Metcalfe.[14] The clinician will find this review especially helpful when discussing with patients the relative utility and indication for bone marrow biopsy. Thankfully, there is an improved blood test for c-kit by high-sensitivity PCR that can detect many, but not all, cases of mastocytosis without the need for bone marrow biopsy.

The treatment review by Castells and Butterfield[15] is of special importance to the clinician managing patients with mast cell disorders, because it provides extensive discussion of the first-, second-, and third-line options in treatment. For patients whose symptoms are not controlled with first-line medications, there are often barriers to treatment with medications for off-label use, or that are not approved in the United States (therefore requiring compounding or foreign sourcing). Numerous case reports suggest that off-label use of omalizumab is beneficial, and a follow-up report in this issue by Constantine et al[16] confirms its efficacy and safety for long-term management and prevention of anaphylaxis in mastocytosis. Increased understanding of mast cell receptors and their ligands, and their signaling pathways, may provide additional targets for therapeutic intervention. However, the management of patients with mastocytosis goes beyond medications and control of symptoms. The article by The Mastocytosis Society reminds us of the many other needs of these patients, including awareness and screening for osteoporosis.[17]

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, we can see how complex the issues surrounding mast cell disorders have become and, despite the remarkable advances of the past decade, we recognize how much more work there is to be done. For example, there are many other active mediators released by mast cells, but in most cases we do not fully understand their role in these conditions, there are no routinely available laboratory tests for them, and we do not have blockers for them that would permit us to confirm the diagnosis in, and more effectively treat patients with MCAS. Also, we do not yet know whether, and to what extent, the risk of anaphylaxis is increased in patients with alpha-tryptasemia, and in other patients with modestly elevated tryptase levels but no evidence of mast cell disease. Prospective evaluation and monitoring of patients with suspected MCAS must be conducted and reported to understand the heterogeneity and natural history of the disease, and the most appropriate use of possible therapeutics. And finally, there is a need for improved treatment options with greater efficacy and/or safety for the prevention of anaphylaxis and other manifestations of these conditions. This will require controlled trials in well-defined patient populations to enable regulatory approval of this new indication for new or existing treatments.

"A house of mirrors, a traditional attraction at amusement parks, is a maze-like puzzle with mirrors as obstacles, and glass panes to parts of the maze they cannot yet get to" (Wikipedia). The analogy of mast cell disorders with a "house of mirrors" is quite apt. It seems everywhere we look we see mast cell disorders, things that look like mast cell disorders, and reflections of mast cell disorders, but not all of them are what they seem and we see things we cannot yet explain. There is a path through the mirrors, and it is with well-designed research studies. We must endorse Valent et al's "call for research" with enthusiasm.

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