Nonclonal Mast Cell Activation Syndrome

A Growing Body of Evidence

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KEYWORDS

• Mast cell activation syndrome • Tryptase • Histamine • Prostaglandin
• Mastocytosis • Mast cell • Flushing

KEY POINTS

- Patients who present with typical features of mast cell activation with laboratory confirmation and without evidence of a clonal mast cell disorder or other medical condition should be initiated on medical treatment to block mast cells and their mediators.
- If a major response is achieved, a diagnosis of nonclonal mast cell activation syndrome (NC-MCAS) is likely and treatment should be optimized, including management of any associated conditions.
- In this review, the latest evidence with regard to the diagnosis and treatment of NC-MCAS is presented.

INTRODUCTION

Over the last decade, recognition of a unique syndrome has emerged in clinical practices and in the literature. These patients present with a unique constellation of signs and symptoms suggesting primary mast cell activation, such as systemic mastocytosis (SM), but without fulfilling the established criteria (Fig. 1). Furthermore, these patients do not have primary allergic disorders to better explain their presentation, such as immunoglobulin E (IgE)–mediated allergy, chronic idiopathic urticaria, or idiopathic anaphylaxis (examples of secondary mast cell activation). Other medical inflammatory conditions, autoimmune diseases, malignant processes, and infections have been ruled out. Although objective markers for this disorder are lacking at this time, patients are diagnosed with idiopathic mast cell activation syndrome (MCAS) and have greatly benefitted from specific treatments that work to block the mast cell mediators. In this review, the diagnosis and treatment of nonclonal idiopathic MCAS (NC-MCAS) are discussed.

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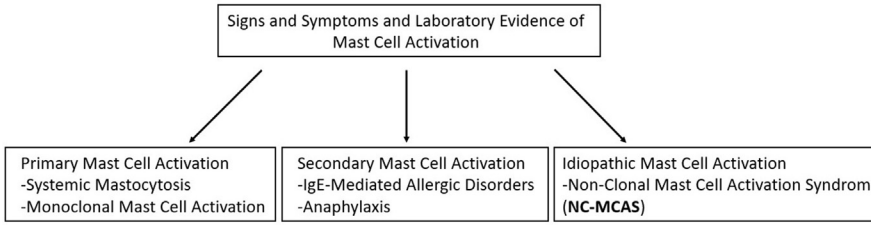

Fig. 1. Classification schemes of mast cell activation disorders. IgE, immunoglobulin E.

BACKGROUND AND PROPOSED MECHANISMS

The mast cell is a complex immune cell that in its mature form resides in the tissues that interact with the external environment, such as the air passageway, skin, and gastrointestinal tract. Although best known for its central role in allergy, anaphylaxis, and asthma, mast cells primarily function in host defense to bacteria, parasites, and viruses (reviewed in[1]). Although a full explanation for the mechanisms that drive activation of mast cells is beyond the scope of this review, it is important to highlight the diversity of receptors and mediators that mast cells may release that characterize the diverse aspects of mast cell activation. Although mast cells exhibit plasticity in development and in response to various stimuli, they generally express the high affinity IgE receptor and low affinity IgG receptor, receptors for complement, proteinase-activating receptors, and pathogen-specific receptors, such as toll-like receptors. On activation, mast cells release a variety of preformed mediators housed in the cytosol granules, including proteases (tryptase, chymase), histamine, newly generated lipid mediators including prostaglandins and leukotrienes, and more than 30 cytokines and chemokines that may be synthesized and released (reviewed in[2]). These mediators that are released either in total (eg, anaphylaxis) or piecemeal[3] carry out a wide array of pathophysiologic functions, including dilation of blood vessels, stimulatory and inhibitory interactions with nerves, physiologic shifts in electrolytes and fluids, and serving as a chemoattractant for other immune cells (eg, neutrophils).

The pathologic hallmark of NC-MCAS is inappropriate activation of mast cells to stimuli that otherwise would be tolerated if not in the activated or reactive state. This inappropriate activation may occur because of altered threshold for activation, aberrant expression of receptors and mediators shifted toward an allergic immune response, or changes in the tissue environment that affect the expression and function of the mediators.[4] There may also exist defects or changes in downstream signaling pathways for mast cell activation (reviewed in[5]). The genetic basis for NC-MCAS is not well understood, but a team of investigators has identified many mutations in the KIT receptor (responsible for proliferation and retention of mast cells in the tissues) and alternative splicing variants in the CD117+ peripheral blood cells of patients with NC-MCAS.[6]

CLINICAL FEATURES

It has become apparent that there is a typical constellation of signs and symptoms of mast cell activation that suggest NC-MCAS and then a smattering of other features that may be more unique to an individual. Many of these classic symptoms have been long appreciated in patients with SM. These symptoms are necessary for the diagnosis (**Box 1**) and include signs and symptoms involving the skin (flushing, pruritis, urticaria, sweating, localized swelling), the air passageway and lungs (rhinitis, throat