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Demystifying Mast Cell Activation Syndrome: A Comprehensive Look at Diagnosis, Management, and Geographic Disparities

Abdulaziz Alshamlan[1] Vikram Anumakonda[1*]

[1]The Dudley Group NHS Foundation Trust, UK.

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Corresponding Author: Vikram Anumakonda FRCP, FFICM, Consultant Physician, Department of Acute Medicine and Critical Care, The Dudley Group NHS Foundation Trust, UK.

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Abstract

Mast Cell Activation Syndrome (MCAS) is a challenging condition where mast cells release mediators inappropriately, causing a variety of symptoms across multiple organ systems. Patients often experience spontaneous and episodic anaphylactic reactions affecting at least two different organ systems at the same time. These symptoms stem from the abnormal activation of mast cells, making diagnosis and management difficult. Current treatments, such as antihistamines and mast cell stabilizers, provide symptom relief but do not cure the condition. There's a pressing need for more research to develop targeted therapies that address the root causes of MCAS.

Involving patients in research significantly improves the accuracy and relevance of the data collected. By adopting a patient-centered approach, we ensure that their experiences and needs are at the core of the research process. This leads to more meaningful outcomes that can better address the challenges faced by those living with MCAS. Future studies should focus on understanding the prevalence of MCAS, improving diagnostic methods, and exploring new treatments to enhance the quality of life for affected individuals.

Introduction

Mast Cell Activation Syndrome (MCAS) is a complex condition characterized by the abnormal release of mast cell mediators, leading to a range of symptoms that can affect multiple organ systems. This can result in patients experiencing spontaneous and episodic anaphylactic manifestations that simultaneously impact at least two different organ systems. The primary cause of these symptoms is the inappropriate release of mediators from mast cells. Mast cell disorders, including MCAS, present with signs and symptoms caused either by the activation of mast cells or by mast cells infiltrating organs and interfering with their normal function.**[1]** Normally, mast cells become active and release mediators as part of their immune function; however, in MCAS, these mediators are released inappropriately, causing a wide array of symptoms across different parts of the body at the same time.**[2]**

Evolution of Our Understanding of Mast Cell Activation Syndrome

The journey to understanding mast cell diseases began long before the discovery of mast cells themselves. In 1869, a cutaneous disease resembling urticaria, known as urticaria pigmentosa, was described. A decade later, in 1879, mast cells were discovered, and it was found that these urticaria pigmentosa lesions contained accumulations of mast cells.**[3]**

Initially, this accumulation of mast cells in the skin was termed mastocytosis and was thought to be confined to the skin. However, in 1949, a case report revealed systemic involvement of mastocytosis, indicating that the disease was not limited to the skin.**[4]**

The understanding of mastocytosis continued to evolve, with the recognition that systemic mastocytosis could present with or without skin involvement.**[5]** In 1984, a case report was published discussing in detail the clinical signs, symptoms, and laboratory findings of a patient who was labeled as having systemic mastocytosis.**[6]** Sonneck et al published case reports of patients who were assessed due to having hypotensive symptoms after wasp or bee stings, half the patients were confirmed to have mastocytosis on assessment of bone marrow, and the other half did not meet their diagnostic criteria of mastocytosis, therefore might be labeled as having “Mast cell activation syndrome” (MCAS). This was the beginning of the thought that systemic mastocytosis can exist without a neoplastic background of mast cells, ie what is known now as “Mast cell activation syndrome” (MCAS).**[7]**

By 1988, research papers began discussing carcinoid syndrome and disorders of systemic mast cell activation together, due to their similar clinical features. **[9]** This comparison highlighted the complexity of mast cell diseases and the need for a deeper understanding of their presentations.

The World Health Organization (WHO) published diagnostic criteria and a classification system for mastocytosis in 2001, distinguishing between cutaneous mastocytosis and systemic mastocytosis, with further subdivisions **[10]**. In the same year, a consensus proposal for the diagnostic criteria and classification of mastocytosis was also published, which included a discussion on differential diagnoses **[11]**.

Initially, various conditions, including mastocytosis and allergic diseases, were categorized under "Mast Cell Disease." After 2010, the term "Mast Cell Activation Syndrome" (MCAS) emerged as a distinct diagnosis **[8]**. These

conditions, involving abnormal mast cell activation, are now recognized as a spectrum of diseases rather than a single disorder.

Valent et al Consensus

Akin et al., in 2010, classified diseases associated with mast cell activation into three categories: primary (including mastocytosis with hypotension or monoclonal mast cell diseases "MMAS"), secondary (encompassing allergic disorders, mast cell activation due to chronic inflammatory or neoplastic disorders, physical urticarias, or chronic autoimmune urticaria), and idiopathic (including anaphylactic reactions, angioedema, urticaria, or mast cell activation syndrome "MCAS"). This classification marked the first introduction of the "idiopathic" MCAS category.**[12]**

The idiopathic classification of this entity has not garnered widespread acceptance as a diagnosis. Consequently, three criteria have been proposed, alongside the exclusion of primary and secondary causes, as necessary for diagnosing mast cell activation syndrome (MCAS). These criteria encompass symptoms consistent with mast cell activation affecting at least two bodily systems, a reduction in frequency or severity upon administration of anti-mediator therapy (such as antihistamines), and an elevation in serum or urinary markers indicative of mast cell activation. **[13,14]**

The diagnostic criteria have been further specified to include typical clinical symptoms, such as flushing, pruritus, and angioedema, as well as an increase in serum total tryptase by 20% above baseline + 2ng/ml (during a symptomatic period or within 4 hours), and response of clinical symptoms to histamine-1/2 receptor blockers or mast cell targeting agents.**[15]** If all of these criteria are met, then the condition would be attributed to systemic mast cell activation.

The clinical manifestations of mast cell activation disorders result from mediators released by mast cells, such as histamine, leukotriene-C4, and prostaglandin D2. While many of these mediators are also produced by other cells like basophils, tryptase is predominantly produced by mast cells. Consequently, tryptase is preferred in diagnostic criteria for MCAS.**[15]**

The clinical response would be achieved by the use of drugs other than antihistamines, but this response is not necessarily an indication of mast cell involvement as many cells will respond to agents like corticosteroids and cyclooxygenase and symptoms will resolve. Therefore, response to histamine receptor blockers is preferred in the diagnosis of Mast cell activation syndrome “MCAS”.

Valent et al. proposed that achieving the above criteria proves systemic mast cell activation, which is not a final diagnosis. The next step is to investigate and differentiate between a primary mast cell activation syndrome (ie monoclonal mast cell diseases “MMAS”), secondary mast cell activation syndrome (like allergies), or idiopathic mast cell activation syndrome “IMCAS” (non-clonal nor trigger mediated) **[15,16]**. They proposed a global classification of mast cell disorders, which is an extension of WHO’s classification of mast cell disorders. This included Mastocytosis (Systemic, Cutaneous, Mastocytoma, and Mast cell sarcoma), Mast cell activation syndrome (as described above), and Myelomastocytic conditions.

In 2011, Molderings et al. proposed another classification of what they labeled mast cell activation disease (MCAD). This first category was systemic mastocytosis (SM), which included conditions that meet WHO criteria. The second category was mast cell activation syndrome (MCAS), which included the conditions that fail to meet WHO criteria for systemic mastocytosis (SM) but present with a clinical picture consistent with mast cell mediator induction. The final category is mast cell leukemia (MCL).**[17]**

Benefits of Unified Classification

A unified classification system for mast cell disorders, including Mast Cell Activation Syndrome (MCAS), offers several key benefits. Firstly, it improves the diagnostic process by providing clear and standardized criteria, leading to more accurate diagnoses and appropriate treatment plans. This reduces the risk of misdiagnosis and ensures that patients receive the most effective interventions. Secondly, a unified system allows for the consistent documentation and reporting of clinical findings, facilitating better interpretation of cases. This standardization is crucial for advancing research, enhancing our understanding of mast cell disorders, and developing new therapeutic strategies. Furthermore, it fosters collaboration among healthcare professionals and researchers, promoting the sharing of knowledge and best practices.

United States

Currently, evidence-based medicine classifies mast cell disorders into primary, secondary, and idiopathic types, using all the previously mentioned diagnostic criteria for diagnosis. Episodic manifestations involve at least two of the specified organ systems such as the skin, upper or lower respiratory systems, gastrointestinal tract, or cardiovascular system. Mere subjective symptoms like fatigue or difficulty concentrating, in the absence of objective, are not considered sufficient. Furthermore, the guidelines stress the importance of evidence linking the timing of symptoms to systemic mast cell-mediator release. This ideally should be documented on multiple occasions, particularly in cases of frequent recurrent episodes. Serum total tryptase is highlighted as a specific marker for mast cell activation, with an increase above a certain threshold deemed indicative of such activation. Lastly, response to medications targeting mast cell stabilization, reduction of mediator production, release inhibition, or mediator action inhibition are the therapeutic options that are being targeted.

Prevalence

The data on the prevalence of MCAS is very limited. In Europe, MCAD affects at least 1 in 364,000 people. In Germany, the prevalence of MCAS was reported to be around 17% in 2013. However, since these figures are based on a limited number of cases, they are likely underestimating the true prevalence of both MCAD and MCAS. A recent study concluded that 4.4% of patients who were suspected to have mast cell disorder have been confirmed to have idiopathic MCAS and 3.4% suspected to have MCAS due to the lack of fulfilling 1 or 2 of the diagnostic criteria.**[21]** It also reported that 12.3% of patients with idiopathic anaphylaxis have been diagnosed with MCAS. A retrospective study revealed that only 2% of MCAS cases were definitively diagnosed, with the majority who reported signs and symptoms remaining suspected due to their significant clinical overlap with other conditions.**[22]**

There is also some evidence suggesting that mast cell activation could be a contributing factor to various clinical conditions, such as fibromyalgia and irritable bowel syndrome, which emphasizes that the currently reported prevalence of MCAS could be underestimated.**[23,24]** Moreover, due to the

rarity of MCADs in comparison to other systemic diseases, it can be easily overlooked which is another factor contributing to the underestimation of the disease prevalence.**[25]** MCAS is believed to be more common than Mast cell leukemia (MCL) and Systemic mastocytosis (SM).

The prevalence of mast cell activation disorder in the United States is not well-established, but research suggests that it may be more common than previously believed.**[26]** According to a survey conducted by The Mastocytosis Society, a US-based patient advocacy organization, 420 respondents reported being diagnosed with mast cell disorders such as mastocytosis or mast cell activation syndrome. Among the participants, 12.4% reported being diagnosed with MCAS, and 4.5% reported being diagnosed with idiopathic anaphylaxis. However, it is important to note that this survey does not represent the entire US population, as it only included patients with known mast cell disorders.

Etiology

In a study, when the prevalence of suspected MCAD was examined based on the symptoms reported by first-degree relatives of MCAD patients and compared with the general population, a marked difference was noted. The prevalence was around 46% among the relatives, in contrast to approximately 17% in the general population in Germany.**[20]** This pronounced difference suggests that beyond environmental influences, genetic factors may play a substantial role in the familial transmission of MCAD.

Clinical Presentations

Mast cells, derived from pluripotent hematopoietic progenitors in the bone marrow, undergo differentiation and proliferation in various peripheral tissues including the skin, gastrointestinal tract, liver, and spleen. This differentiation results in distinct mast cell phenotypes. These phenotypic variations underpin the heterogeneous clinical manifestations of mast cell activation syndrome (MCAS), characterized by the release of mediators such as histamine, leukotrienes, and cytokines.**[27]**

Clinically, MCAS can present with symptoms including pruritus, flushing, gastrointestinal distress, headaches, and neuropsychiatric disturbances, which are contingent on the affected tissue and mediator profile. There is a particularly high concentration in the skin and mucosal linings. This abundance makes the respiratory and gastrointestinal tracts more susceptible to clinical manifestations of MCAS.**[28]**

Patients presenting with a constellation of symptoms such as flushing, itching, unexplained systemic hypotension or fluctuating blood pressure, and unexplained gastrointestinal disturbances typically undergo an initial evaluation to rule out common causes. If the primary evaluations do not reveal a clear cause, the patient is usually referred for further investigation to determine if there is an allergic basis for their symptoms. Should the workup for an allergic cause come back negative, the next logical step is to consider the possibility of an unrecognized mast cell proliferative disorder.**[29]**

Dermatological manifestations such as pruritus, angioedema, and flushing are the most common signs and symptoms of MCAS.**[21]** Gastrointestinal involvement is the second most common manifestation of MSAS, with patients frequently experiencing diarrhea, abdominal pain, gastroesophageal reflux disease, bloating, and nausea/vomiting. **[21]** Cardiovascular symptoms can include hypotension and tachycardia. Respiratory symptoms often associated with MCAS are wheezing, cough, runny nose, nasal congestion, dyspnoea, and non-ischemic chest pain. These symptoms are often episodic and can be triggered by various stimuli, such as allergens, exercise, and stress. Some individuals with MCAS may also present with recurrent episodes of bronchospasm, like asthma exacerbations.**[30]** Other symptoms such as bone and muscle aches, headaches, anxiety, and fatigue are also prevalent. Anaphylaxis, a severe and potentially life-threatening allergic reaction, is one of the most serious manifestations of MCAS. It often involves rapid onset symptoms affecting the skin or mucosal tissues and can include systemic manifestations.

The symptoms of MCAS are known to fluctuate over time, with their severity ranging from mild to severe. This variability and potential severity can significantly impact the daily lives of individuals with MCAS, as well as their families and caregivers, underscoring the complexity and multi-system involvement of this condition.

Sonneck et al. paper discussed cases of severe hypotension following wasp or bee stings, where no specific IgE was detectable, yet half of the patients showed high tryptase levels, and bone marrow examinations confirmed systemic mastocytosis. This highlighted the importance of considering mast cell diseases in patients with severe allergic reactions without clear triggers.**[31]**

Diagnosis

MCAS primarily impacts people who experience episodes of mast cell activation without identifiable mast cell abnormalities or external triggers. It is diagnosed by excluding other primary and secondary mast cell activation disorders, as well as idiopathic anaphylaxis, before confirming MCAS. **[2]** Also, response to treatments targeting the heightened mediator is an essential part of diagnosing MCAS as mentioned above.

It is important not to dismiss a patient based on low tryptase levels since many individuals with Mast Cell Activation Syndrome (MCAS) do not exhibit elevated tryptase. In fact, 85% of those with confirmed mastocytosis show increased tryptase levels, while there are 25% show low levels. The current tryptase measurement is not an entirely conclusive diagnostic tool. Additionally, there is ongoing development of new tests aimed at providing more accurate and reliable blood investigations for diagnosing various forms of mast cell activation.**[32]** Calculating the Tryptase Depletion Index (TDI) from gastrointestinal biopsies is a new additional proposed diagnostic tool for MCAS.**[33]**

Management and Treatment

The treatment of acute MCAS episodes should follow anaphylaxis guidelines, with epinephrine being the first line of treatment if indicated by the severity of symptoms.**[34]**

Chronic management of MCAS is multi-factorial. Antihistamines and mast cell stabilizing agents are mainstays in the management of mast cell activation syndrome MCAS. **[2,17,35]** Other agents such as prednisolone, cyclosporine, methotrexate, and azathioprine can be considered.**[36]** Moreover, anti-IgE has also been shown to lessen symptoms of mast cell activation disease (MCAD) **[37]**. For example, Omalizumab, which blocks the binding of IgE to its receptors, has been reported to reduce mast cell reactivity and sensitivity to activation, potentially reducing anaphylactic episodes.**[34]**

Mast cells respond to cytokines, and interventions such as interferon alfa-2b could reduce spontaneous degranulation of mast cells. This is a potential treatment option that aims at controlling the underlying mechanisms of mast cell activation.**[27]**

Conclusion

Mast Cell Activation Syndrome (MCAS) remains a complex and multifaceted disorder, impacting multiple organ systems through the inappropriate release of mast cell mediators. While significant progress has been made in understanding and classifying mast cell disorders, substantial gaps remain in the epidemiology, diagnosis, and management of MCAS. Current data on the prevalence and incidence of MCAS are limited and often underestimated due to diagnostic ambiguities and clinical overlaps with other conditions. Furthermore, existing diagnostic criteria, although helpful, are not universally accepted and require refinement to improve accuracy and reliability.

The management of MCAS presents additional challenges, given the variability in symptom presentation and response to treatment. Current therapeutic strategies, primarily involving antihistamines and mast cell stabilizers, offer symptom relief but are not curative. More research is needed to develop targeted therapies that address the underlying pathophysiology of MCAS.

Future studies should focus on the prevalence and incidence of MCAS in diverse populations, the development of more precise diagnostic tools, and the efficacy of novel therapeutic interventions. By advancing our understanding of MCAS, we can improve patient outcomes and enhance the quality of life for those affected by this debilitating condition.

An innovative and proactive approach involving patients in mast cell disorders research makes the data we collect much more accurate and relevant. By prioritizing a patient-centred and patient-driven approach, we make sure that their perspectives, experiences, and needs are at the heart of the research, leading to outcomes that are more meaningful and impactful.

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