Special Article

Proposed Diagnostic Algorithm for Patients with Suspected Mast Cell Activation Syndrome

Peter Valent, MD, Cem Akin, MD, PhD, Patrizia Bonadonna, MD, Karin Hartmann, MD, Knut Brockow, MD, Marek Niedoszytko, MD, PhD, Boguslaw Niedoszytko, PhD, Frank Siebenhaar, MD, Wolfgang R. Sperr, MD, Joanna N.G. Oude Elberink, MD, PhD, Joseph H. Butterfield, MD, Olivier Hermine, MD, PhD, Jason Gotlib, MD, MS, Sigurd Broeysbs-Olsen, MD, PhD, Alberto Orfao, MD, PhD, Hans-Peter Horny, MD, Massimo Triggiani, MD, PhD, Michel Arock, PharmD, PhD, Lawrence B. Schwartz, MD, PhD, and Dean D. Metcalfe, MD, PhD

Mast cell activation (MCA) accompanies diverse physiologic and pathologic processes and is one of the more frequently encountered conditions in medicine. MCA-related symptoms are usually mild and often transient. In such cases, histamine receptor blockers and other mediator-targeting drugs can usually control MCA. In severe cases, an MCA syndrome (MCAS) may be diagnosed. However, overt MCAS is an unusual condition, and many patients referred because of suspected MCAS are diagnosed with other diseases (autoimmune, neoplastic, or infectious) unrelated to MCA or suffer from MCA-related (eg, allergic) disorders and/or comorbidities without fulfilling criteria of an overt MCAS. These considerations are important as more and more patients are informed that they may have MCA or even MCAS without completing a thorough medical evaluation. In fact, in several instances, symptoms are misinterpreted as MCA/MCAS, and other clinically relevant conditions are not thoroughly pursued. The number of such referrals is increasing. To avoid such unnecessary referrals and to prevent misdiagnoses, we propose a diagnostic algorithm through which a clinically relevant (systemic) MCA can be suspected and MCAS can subsequently be documented or excluded. In addition, the algorithm proposed should help guide the investigating care providers to consider the 2 principal diagnoses that may underlie MCAS, namely, severe allergy and systemic mastocytosis accompanied by severe MCA. Although validation is required, we anticipate that this algorithm will facilitate the management of patients with suspected MCAS. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1125-33)

Key words: Mast cells; MCAS; Diagnostic algorithm; Tryptase; KIT D816V

INTRODUCTION

Mast cells (MCs) are multifunctional effector cells involved in innate and acquired immunity and attendant inflammatory responses. They consist of precursors in the bone marrow that differentiate into mature tissue-resident cells after exposure to colony-stimulating factors

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INTRODUCTION

Mast cells (MCs) are multifunctional effector cells involved in innate and acquired immunity and attendant inflammatory responses. They consist of precursors in the bone marrow that differentiate into mature tissue-resident cells after exposure to colony-stimulating factors.
is severe, an MCA syndrome (MCAS) may be diagnosed. In events. When MC involvement is documented and the reaction (3) when comorbidities make the patient less tolerant to MCA MCs is high, (2) when MCs are in a even life-threatening MCA may develop when (1) the burden of comorbidities, other patient-related factors (alcohol, nicotine, or allergen(s), the type and amount of IgE, the presence of comorbidities, other patient-related factors (alcohol, nicotine, or illegal substances), the type and amount of coactivating (priming) cytokines and chemokines, and the reactivity of organ systems to these mediators. The ability of MCs and basophils to secrete mediators of anaphylaxis in response to a specific agonist, often referred to as “releasability,” depends on several factors, including the underlying condition (disease), the number and type of involved receptors, the signaling molecules engaged, and the genetic background of the individual. The severity of a resulting reaction is also influenced by the number of MCs (and basophils) involved in the event, the nature and number of IgE-reactive allergen(s), the type and amount of IgE, the presence of comorbidity, other patient-related factors (alcohol, nicotine, or illegal substances), the type and amount of coactivating (priming) cytokines and chemokines, and the reactivity of organ systems to these mediators.

MC activation (MCA) can be documented in a number of physiologic and pathologic conditions. Acute MC is thus encountered in IgE-mediated allergic reactions, and in extreme instances may result in systemic anaphylaxis. Severe or even life-threatening MCA may develop when (1) the burden of MCs is high, (2) when MCs are in a “hyperactivated” state, and (3) when comorbidity makes the patient less tolerant to MCA events. When MC involvement is documented and the reaction is severe, an MCA syndrome (MCAS) may be diagnosed. In the past 50 years, clinical symptoms resulting from MCA have primarily been documented in the context of allergic diseases. More recently, however, MCA has also been considered in the context of MC neoplasms. This article is a discussion of the complexity of MCA syndrome and MCA. MC and MCAS have been delineated by a consensus group. However, some constellation still remains over the diagnosis of MCAS, and many patients are referred because they believe they have MCAS or their doctors judged that the symptoms reported could be indicative of MCA or MCAS. To address this challenge, our group has worked on a diagnostic algorithm for patients with suspected MCAS. This algorithm is presented herein, together with associated criteria, assays, and tools that will assist in the diagnosis of MCA and MCAS.

**TABLE I. Consensus criteria for MCAS**

| Criterion A: Typical clinical signs of severe, recurrent (episodic) systemic MCA are present (often in form of anaphylaxis) (definition of systemic: involving at least 2 organ systems) |
| Criterion B: Involvement of MC is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual’s baseline to plus 20% + 2 ng/mL |
| Criterion C: Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production, or drugs blocking mediator release or effects of MC-derived mediators |

*The consensus criteria for MCAS were first published in Valenta et al. All 3 MCAS criteria (A+B+C) must be fulfilled to call a condition MCAS. (Other MC-derived markers of MCA (histamine and histamine metabolites, PGD2 metabolites, and heparin) have also been proposed, but are less specific compared with tryptase.)

Example: histamine receptor blockers.

**CONSENSUS CRITERIA AND CLASSIFICATION OF MCAS**

When MCA symptoms are severe and recurrent, the diagnosis of MCAS must be considered. As per existing consensus criteria, the term MCAS applies when (1) typical clinical signs of severe recurrent acute systemic MCA are present (especially in the form of clinical features and findings of anaphylaxis), (2) the involvement of MCs can be demonstrated by biochemical analyses (preferably through an increase in tryptase following the 20% + 2 formula as discussed later), and (3) the symptoms respond to treatment with MC-stabilizing agents or drugs targeted against MC mediator production, secretion, or receptor binding. All 3 criteria must be met to establish the diagnosis of MCAS (Table I). On the basis of the underlying condition, patients with MCAS should then be further classified into (1) those with primary MCAS, where KIT-mutated, clonal (CD25+) MCs are detected (with or without an underlying diagnosis of mastocytosis); (2) those with secondary MCAS, where an underlying nonneoplastic disease, usually an IgE-dependent allergy or other hypersensitivity reaction, is detected; and (3) those with idiopathic MCAS, where no KIT-mutated MCs and no overt inflammatory disorders (that may explain MCA) are detected, and no trigger for a hypersensitivity reaction is found (Table II). In a considerable number of patients with MCAS, several factors act together to cause severe or even life-threatening anaphylaxis. For example, in patients with systemic mastocytosis (SM) and MCAS, an IgE-dependent allergy (eg, against insect venom) is frequently documented. These patients suffer from a combination of primary and secondary MCAS, and, as a result, they are at high risk to develop recurrent life-threatening anaphylaxis. These patients require special attention and personalized therapy and are usually regarded as candidates for lifelong immunotherapy and may additionally require omalizumab therapy and/or other pharmacologic intervention. Detailed knowledge about the etiology and the complexity of MCAS is thus important and forms the basis for establishing the exact diagnosis and developing an optimal treatment plan.
**TABLE II.** Recognized variants of MCAS and diagnostic features

<table>
<thead>
<tr>
<th>Variant of MCAS</th>
<th>Main diagnostic features</th>
</tr>
</thead>
</table>
| Primary MCAS (clonal MCAS)            | The KIT D816V mutation is detected and MCs aberrantly display CD25 in most cases (a) with confirmed mastocytosis (CM or SM)\(\dagger\)
|                                       | (b) with only 2 minor SM criteria                                                        |
| Secondary MCAS                        | An IgE-mediated allergy, another hypersensitivity reaction, or another immunologic disease that can induce MCA, and thus MCAS, is diagnosed, but no neoplastic MC or KIT D816V is found\(\dagger\) |
| Idiopathic MCAS                       | Criteria to diagnose MCAS are met, but no related reactive disease, no IgE-dependent allergy, and no neoplastic/clonal MCs are found\(\dagger\) |

\(\dagger\)The terms clonal MCAS and monoclonal MCAS (MMCAS) can be used synonymously with the term primary MCAS.

\(\dagger\)Most of the patients suffer from CM or SM. However, in some cases, only 2 minor SM criteria are detected and criteria for SM and CM are not fulfilled.

\(\dagger\)No KIT mutation at codon 816 is detected, and flow cytometry (if performed) will not detect a clonal population of CD25\(^+\) MCs.

**TABLE III.** Clinical symptoms typically associated with local or systemic MCA

<table>
<thead>
<tr>
<th>Acute episodic symptom</th>
<th>Typical for MCA</th>
<th>MCAS more likely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Flushing</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Pruritus</td>
<td>+</td>
<td>+/–</td>
</tr>
<tr>
<td>Angioedema</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>+/–</td>
<td>–</td>
</tr>
<tr>
<td>Nasal pruritus</td>
<td>+/–</td>
<td>–</td>
</tr>
<tr>
<td>Wheezing</td>
<td>+</td>
<td>+/–</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>+/–</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>+/–</td>
<td>–</td>
</tr>
<tr>
<td>Hypotensive syncope</td>
<td>+/–</td>
<td>+</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>+/–</td>
<td>+</td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>+/–</td>
<td>+/–</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>+/–</td>
<td>+/–</td>
</tr>
</tbody>
</table>

+++ Higher specificity; +, moderate specificity; +/–, low specificity; –, not considered to be indicative of MCAS (as single symptom).

*Note.* To count as indication of MCA, these symptoms need to be episodic and recurrent and cannot be explained by other known disorders or conditions (other than MCA).

**SYMPTOMS PRODUCED BY SYSTEMIC MCA**

Symptoms of MCA are among the most frequently recorded and treated symptoms in the daily practice of applied medicine. MCA-related symptoms range from mild to severe, and may at times be life-threatening, especially in patients with mastocytosis and concomitant allergy. MCA symptoms are caused by several different vasoactive and proinflammatory mediators released from MCs when these cells are activated by an allergen via IgE receptor cross-linking or other mechanisms.\(^1\,2\,6\,26\,27\,37\) As a result, the severity of MCA correlates with the extent of mediator release from MCs during an anaphylactic reaction. Well-recognized symptoms of systemic MCA include, among others, acute urticaria, flushing, abdominal cramping, diarrhea, hypotensive syncope or near syncope, and tachycardia (Table III)\(^1\,3\,26\,28\,37\). Although none of these symptoms is completely specific for MCA, 1 or more are typically detected in these patients. The likelihood of MCA increases when 2 or more of such symptoms are documented, and the likelihood is even higher when the symptoms respond to agents blocking mediator effects, mediator production, or mediator secretion. Indeed, the response to such drugs is helpful in practice and is therefore a criterion of MCAS.\(^26\,28\) Another important aspect is that several different mediators may be involved in MCA-related symptomatology\(^1\,6\,26\,27\,31\) (Table IV). In fact, depending on the organ and pathology involved, certain MC products may act as critical inducers of MCA, and sometimes treatment may need adjustment because of the effects of such mediators. Likewise, vascular instability may be triggered not only by histamine but also by prostaglandins (PGs) and/or leukotrienes (LTs) derived from activated MCs in the same patient, so that the reaction can be managed when administering histamine receptor blockers and PG/LT synthesis inhibitors and/or receptor blockers.\(^32\) Other potentially relevant mediators associated with activation of MCs are platelet-activating factor, tryptases, and various cytokines\(^20\,31\,33\,35\) (Table IV).

MCA may also develop with chronic and/or a less severe symptomatology (Table V). In such patients, the symptoms are often less specific and include headache, nausea, and nonspecific gastrointestinal complaints.\(^31\) It is important to state that these symptoms alone are not regarded criteria of severe systemic MCA or MCAS. Nevertheless, such symptoms may possibly relate to local MCA, and thus the administration of anti—mediator-type drugs or MC-stabilizing agents may be considered. However, it is of utmost importance to be aware that there are a number of diseases and conditions in the differential diagnoses that must be taken into account in such cases, including psychiatric, cardiovascular, infectious, endocrinologic, gastrointestinal, toxic, and oncologic disorders. In some patients, no definitive organic diagnosis will be made during the initial evaluation, and follow-up will be necessary to watch for the evolution of a diagnosable disorder.

All in all, MCA can be divided into severe and less severe types, into acute, episodic, and chronic forms, and into systemic and local variants (Table V). However, severe MCA fulfilling MCAS consensus criteria is almost always associated with the occurrence of acute severe recurrent symptoms affecting more than 1 organ or tissue, often with severe hypotension and anaphylaxis.\(^26\,28\) In the absence of such a symptomatology, the diagnosis of MCAS is unlikely (Figure 1). There are also frequently reported symptoms (by patients with suspected MCAS) that are not necessarily related to MCA, such as joint hypermobility, sleep disruption, erythromelalgia, burning hands, odor aversion, dysautonomia, obesity, sweating, and anxiety. It may also be that a number of these patients suffer from psychological or psychiatric problems rather than MCA, which may require special attention and appropriate management.

**LABORATORY ASSESSMENTS IN PATIENTS WITH SUSPECTED MCA**

MCA is associated with the release of preformed and newly generated mediators and their effects on various target cells.\(^26\,28\,31\) In severe systemic reactions, increased levels of MC-derived mediators should be measurable in biological fluids.
Some mediators, such as tryptase, are more specific than others for MCs and thereby considered as the most precise parameters for the demonstration and documentation of MCA. However, the sensitivity of the tryptase algorithm decreases with decreasing clinical severity and with delayed blood draws after resolution of clinical symptoms.

Other mediators, potentially more sensitive than tryptase, are less specific because they are also synthesized and released by other cell types. For example, histamine is produced, stored, and released after resolution of clinical symptoms. However, the sensitivity of the tryptase algorithm decreases with decreasing clinical severity and with delayed blood draws after resolution of clinical symptoms.

First, MC involvement should be confirmed by measuring an event-related, transient increase in serum tryptase. This "event-related" increase in tryptase is best captured in a 1- to 4-hour postevent interval during which tryptase remains elevated, and the resulting enzyme level must then be compared with the individual's baseline tryptase. If no previous baseline level is available, the baseline level must be assessed at least 24 to 48 hours after complete resolution of all signs and symptoms.

The other important consideration is what minimal increase in serum tryptase is required to establish it as indicative of severe systemic MCA. The consensus proposal is that a minimal increase in the acute serum tryptase level to greater than plus 20% of baseline + 2 ng/mL absolute tryptase strongly supports the diagnosis of MCAS. For example, if the baseline tryptase level is 5 ng/mL, an increase to more than 8 ng/mL suggests MCA. This approach has recently been validated in the context of mastocytosis (unpublished data) and nonmastocytosis conditions. When the postevent baseline tryptase level remains elevated (>20 ng/mL), a number of underlying disorders have to be considered, including hereditary alpha-tryptasemia, SM, and non-MC lineage myeloid neoplasms (see Table E1 in this article’s Online Repository at www.jaci-inpractice.org).

Additional mediators, when rising from baseline, may also serve as markers of MCA or even MCAS. These include, among others, histamine (plasma, urine), histamine metabolites (urine), and the 24-hour urine PGD2 metabolite, 11β-PGF2α, or the LTC4 metabolite, LTE4, level (urine). However, as noted, these mediators are less specific for MCA compared with tryptase. Moreover, no data are available to establish what minimal increase in these mediators would count as a reliable indicator (and thus criterion) of systemic MCA. It is suggested that an event-related increase in 2 or more of the plasma or urinary histamine metabolites or PGD2 metabolites, or LTE4 of at least 50% from baseline (eg, from 50 to at least 75), could function as an indication of MCA. Another possibility is a determination of a level 2-fold above the upper limit of normal. Measurement of such additional mediators may indeed be helpful in the evaluation of patients with suspected MCA/MCAS, and should therefore be considered, especially when the serum tryptase test is not available or did not produce a convincing result or when no blood (but only urine) could be collected during the event. This is important because other MC mediators are sometimes also relevant clinically, because they can provoke MCA and may lead to adjustments of (individualized) therapeutic approaches. It is also worth noting that PGD2 is primarily synthesized in MCs but not in blood basophils.

### TABLE IV. Clinical effects of MC mediators produced and released during MCA

<table>
<thead>
<tr>
<th>Symptomatology of MCA</th>
<th>Relevant involved mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular instability, hypotension, tachycardia, syncope, anaphylaxis</td>
<td>Histamine, LTC4, LTE4, PGD2, VEGF, PAF, TNF-α</td>
</tr>
<tr>
<td>Enhanced vasopermeability, edema formation in various organs</td>
<td>Histamine, VEGF, LTC4, LTE4, PAF</td>
</tr>
<tr>
<td>Headache and nausea</td>
<td>Histamine</td>
</tr>
<tr>
<td>Fever and chills</td>
<td>TNF-α</td>
</tr>
<tr>
<td>Urticaria, pruritus, flushing</td>
<td>Histamine, VEGF</td>
</tr>
<tr>
<td>Bronchocstriction</td>
<td>Histamine, PGD2, LTC4, LTD4, PAF</td>
</tr>
<tr>
<td>Mucus secretion</td>
<td>Histamine, proteases, PGD2, LTC4</td>
</tr>
<tr>
<td>Nasal congestion, wheezing</td>
<td>Histamine</td>
</tr>
<tr>
<td>Gastric hypersecretion</td>
<td>Histamine</td>
</tr>
<tr>
<td>Abdominal pain and cramping</td>
<td>Histamine, LTC4, PAF</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Histamine</td>
</tr>
</tbody>
</table>

PAF, Platelet-activating factor; VEGF, vascular endothelial growth factor (α=vascular permeability factor).

*Clinical symptoms recorded in patients with MCA and MCAS. In patients with MCAS, more than 1 symptom is typically recorded, and in most patients, hypotension and signs of anaphylaxis are found.

† Some of the clinically most relevant MC-derived mediators are listed. In patients with MCAS, histamine and arachidonic acid derivatives may play a central role. The impact of the other MC-derived mediators, such as PAF, remains at present unknown.

(1) In about 1% of all patients with MCA, severe hypotension is associated with fever.

### TABLE V. Classification of mast cell activation (MCA) and related conditions

(a) According to organ involvement and severity

<table>
<thead>
<tr>
<th>Systemic MCA</th>
<th>Severe systemic MCA (MCAS criteria fulfilled)</th>
<th>Local MCA (mild/moderate or severe) (MCAS criteria not fulfilled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate systemic MCA (MCAS criteria not fulfilled)</td>
<td>Severe systemic MCA = MCAS (MCAS criteria fulfilled)</td>
<td>Local MCA (mild/moderate or severe) (MCAS criteria not fulfilled)</td>
</tr>
</tbody>
</table>

(b) According to underlying condition

<table>
<thead>
<tr>
<th>Primary (clonal) MCA</th>
<th>Cutaneous mastocytosis (CM)</th>
<th>Systemic mastocytosis (SM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-dependent allergy (or atopy)</td>
<td>1-2 minor SM criteria recorded but no SM can be diagnosed</td>
<td>Organ-specific variants</td>
</tr>
<tr>
<td>IgE-independent hypersensitivity reactions</td>
<td>Other conditions</td>
<td>Physical, neurologic, and others</td>
</tr>
</tbody>
</table>

(c) According to frequency and symptom-free interval

<table>
<thead>
<tr>
<th>Episodic recurrent</th>
<th>With a known trigger (eg, allergen)</th>
<th>Without a known trigger</th>
<th>Chronic persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Systemic MCA involves 2 or more organ systems.*
Cell-based assays have also been proposed to evaluate MCA and basophil activation. Reliable and established parameters of basophil activation and MCA include analysis of cell surface levels of CD63 and/or CD203c. Both proteins (antigens) increase on the surface of FcεR cross-linked MCs and basophils. However, although basophils are easily accessible for (repeated) investigations, MCs are not, unless a tissue biopsy specimen is available. In addition, many of the activation-linked surface antigens, including CD63 and CD203c, are upregulated on neoplastic resting MCs in SM. Therefore, MC typing is not recommended as a screening approach to define or quantify MCA. Rather, MC typing is recommended as a diagnostic approach to reveal or exclude the presence of SM in patients with MCA or MCAS.

**PROPOSED DIAGNOSTIC ALGORITHM FOR PATIENTS WITH SUSPECTED MCAS**

When a patient is critically ill and/or presents with moderate to severe hypotension, it is essential to clinically stabilize the patient before exploring etiology. At the same time, the physical examination may reveal the presence of typical skin lesions of mastocytosis. In other cases, the patient or the relatives may inform the emergency team about a known diagnosis of mastocytosis or allergy.

After stabilization, the etiology must be clarified: in the first step, symptoms should be classified as “probably MCA-related” on the basis of clinical features, elimination of other etiologies, and response to certain drugs (Figure 1). In the second step, it is important to screen for multiple underlying disorders, because in patients with MCAS, more than one such underlying disease may be present (eg, mastocytosis and allergy). With regard to mastocytosis, typical indicators are typical skin lesions, a persistently elevated serum tryptase level and detection ofKIT D816V in peripheral blood cells. According to the underlying condition, MCAS is classified into primary (clonal) MCAS, secondary MCAS (usually with an IgE-dependent allergy), and idiopathic MCAS. In patients with clonal MCAS, the final diagnosis may be CM, SM, or monoclonal MCAS defined by 2 (but not more) SM criteria. In a final step, the management and treatment plan is established. MMAS, Monoclonal/primary MCAS.

**FIGURE 1.** Proposed algorithm for patients with suspected MCAS. After the patient has been clinically stabilized, the physician examines potential etiologies and asks for MCAS criteria. When the symptoms are severe and episodic, the likelihood of MCAS is quite high. MCAS consensus criteria are then applied to confirm MC involvement. MCAS criteria can also be applied when the symptoms are less severe and/or atypical. However, in most of these patients, MCAS criteria are not fulfilled. In a next step, the underlying etiology is examined. At this phase of the workup, it is important to screen for multiple underlying disorders, because in patients with MCAS, more than one such underlying disease may be present (eg, mastocytosis and allergy). With regard to mastocytosis, typical indicators are typical skin lesions, a persistently elevated serum tryptase level and detection of KIT D816V in peripheral blood cells. According to the underlying condition, MCAS is classified into primary (clonal) MCAS, secondary MCAS (usually with an IgE-dependent allergy), and idiopathic MCAS. In patients with clonal MCAS, the final diagnosis may be CM, SM, or monoclonal MCAS defined by 2 (but not more) SM criteria. In a final step, the management and treatment plan is established. MMAS, Monoclonal/primary MCAS.
systems. Reporting that such episodes are recurrent increases the likelihood of MCAS (Figure 1). A diagnosis of MCAS is further supported by demonstrating an event-related increase in tryptase and a sustained response to MC-stabilizing drugs or drugs directed against MC mediators. The diagnosis of anaphylaxis does not require these MCAS criteria.

In the final step, after having confirmed the presence of MCA using consensus criteria, the diagnosis of MCAS can be made (Figure 1). For many patients with MCAS, an IgE-dependent allergy is known or will be detected (Figure 1). In others, underlying mastocytosis may be found. When neither is the case, the patient may still suffer from mastocytosis. Indirect signs for the presence of an underlying (occult) SM include an elevated baseline serum tryptase level detected after complete resolution of all symptoms or a D816V KIT mutation in circulating blood leukocytes, blood cell count abnormalities (eg, eosinophilia), symptoms suggestive of SM such as unexplained osteoporosis, gastrointestinal symptoms (diarrhea, abdominal cramps, or malabsorption), or an elevated Red Española de Mastocitosis (REMA) or National Institutes of Health clinical activity score (NIHCAS). A bone marrow investigation may confirm the presence of SM in these patients (Figure 1).

In other patients, clonal KIT-mutated (CD25+) MCs are detected, but only 1 or 2 minor SM criteria and no major SM criterion are found. These patients as well as those with cutaneous mastocytosis (CM) or SM are classified as having primary (clonal) MCAS (Table II). If an IgE-dependent allergy or other underlying reactive disease is present in the absence of clonal MCs, the diagnosis is secondary MCAS (Table II; Figure 1). If no evidence for primary or secondary MCAS is found, the patient is classified as having idiopathic MCAS (Table II; Figure 1).

WHAT IF SYMPTOMS SUGGEST MCA BUT MCAS CRITERIA ARE NOT MET?

In a reasonable number of cases, signs and symptoms of MCA will be detected, but the criteria of MCAS will not be fulfilled. One such cohort consists of patients who present with severe recurrent symptoms and a diagnostic increase in serum tryptase levels, but where treatment with conventional drugs does not lead to a major improvement in symptoms. In these cases, a provisional diagnosis of “possibly MCAS” may be established and further treatment should be introduced.

In other patients, severe symptoms may be recorded, but tryptase levels increase only slightly. In these patients, it is reasonable to determine the levels of additional relevant mediators such as PGD₂, if the test is available. Whenever a major increase in the PGD₂ metabolite level is found and the symptoms respond to cyclooxygenase inhibitors, the diagnosis of MCAS may also be considered although the cell source may be ambiguous, particularly if both tryptase and histamine or histamine metabolite levels are normal. In such patients, the symptoms must be severe and the increase in mediator levels must be substantial.

However, as noted, there are also patients in whom the symptoms are less severe and/or restricted to 1 organ system or even a local organ site. In these patients, it may still be reasonable to ask for MCAS criteria (Figure 1). However, in most of these cases, it will be determined that they are suffering either from an unrelated disease (Table V) or from a less severe form of MCA that does not meet MCAS criteria. These may include patients suffering from less severe allergic reactions or patients with mastocytosis with mild mediator symptomatology. Others may be suffering from food intolerance, drug side effects, toxin exposure, an autoimmune disease, a psychiatric disease, or other, less severe, reactive conditions associated with MCA.

A special situation is when mastocytosis with MCA does not fulfill MCAS criteria. The consensus group has recommended that in cases with mastocytosis (irrespective of the variant), any form of MCA requiring continuous mediator-targeted therapy should be marked by the diagnostic label “SV” that appears as a subscript in the final diagnosis. These patients include those who have MCAS and those who do not have an overt MCAS but suffer from MCA-related symptoms requiring therapy. For example, in a patient with indolent SM (ISM) requiring continuous histamine receptor–targeting agents and glucocorticosteroids to control MCA, the final diagnosis should be ISM₉V even if the criteria of MCAS are not met (or were not documented).

Another special situation is hereditary alpha-tryptasemia, an autosomal-dominant condition defined by germline replications (usually duplications or triplications) of the TPSAB1 gene encoding alpha-tryptase. In affected family members, symptoms of MCA, if present, may be chronic and/or acute, and other symptoms and findings, including dysautonomia, chronic pain, and connective tissue abnormalities such as joint hypermobility, may also be observed.

There are also patients from families in which a slightly elevated tryptase is measured but the genetic (molecular) background remains undefined. It is important to note in this regard that an elevated basal serum tryptase level per se is neither an indication for MCA or MCAS nor is it an a priori risk factor for the occurrence of MCA or MCAS. Rather, an elevated basal tryptase level is found not only in patients with mastocytosis or hereditary alpha-tryptasemia (where the risk for anaphylaxis may be increased), but also in patients with myeloid non–MC lineage neoplasms (see Table E1). In addition, elevated basal tryptase levels are detectable in patients with end-stage kidney disease and some parasitic infections (see Table E1).

DISORDERS UNDERLYING MCA AND MCAS: FINAL DIAGNOSIS

A number of pathologic conditions can be associated with systemic MCA, including allergic reactions, mastocytosis, autoimmune disorders, infectious diseases (eg, infections involving the skin or Helicobacter pylori+ gastritis), and intoxications. The most frequent underlying cause is an IgE-dependent allergy. In contrast, only a few patients will have mastocytosis, which is a rare disease compared with IgE-dependent allergies. However, the prevalence of MCAS is rather high among patients with mastocytosis. The highest prevalence of MCAS appears in patients who suffer from both an IgE-dependent allergy and mastocytosis. The population requiring special attention consists of patients suffering from primary MCAS and insect venom allergy. The induction of long-term tolerance to an insect venom allergen is reduced in primary MCAS, and severe or even fatal reactions after discontinuation of immunotherapy have been described. On the basis of available data, it seems likely that patients with primary MCAS and insect venom allergy are protected only while under continuous venom immunotherapy, which is therefore a recommended approach.
When an IgE-dependent allergy is suspected, a detailed diagnostic evaluation for allergies and an appropriate management plan should be initiated. Similarly, when a clonal MC disease has been identified, the disorder needs to be staged (eg, CM and SM variants). A key diagnostic parameter is a mutational analysis of KIT. In most adults with SM, the D816V KIT mutation will be detected.\textsuperscript{2,3,76} Using a highly sensitive allele-specific quantitative PCR, the mutation can also be identified in the peripheral blood of most patients with SM.\textsuperscript{73-79}

However, in some adults and more commonly in children, other KIT point mutations are found.\textsuperscript{6,80,81} Pediatric patients most commonly have CM. The prevalence of MCAS in pediatric patients is unknown, but both cutaneous and systemic reactions have been reported.\textsuperscript{2,3}

DIFFERENTIAL DIAGNOSES TO MCA AND MCAS

A number of differential diagnoses have to be taken into account in patients with suspected MCAS\textsuperscript{26-28} (see Table E1). In those patients who have severe hypotension and shock resembling anaphylaxis, differential diagnoses (to both, anaphylaxis and MCAS) include, among others, cardiovascular and cerebrovascular disorders, acute endocrinologic emergencies, severe infections (sepsisemia), acute dehydration, drug overdose, exposure to environmental toxins, somatoform disorders, and acute psychiatric events. In other patients, no signs of a severe systemic reaction (and no hypotension) are recorded but the physician is of the opinion that MCAS has to be ruled out. The differential diagnoses in such cases then relate to organ-specific local events, such as acute diarrhea (gastrointestinal diseases or infections), acute psychiatric events. In other patients, no signs of a severe systemic reaction (and no hypotension) are recorded but the physician is of the opinion that MCAS has to be ruled out. The differential diagnoses in such cases then relate to organ-specific local events, such as acute diarrhea (gastrointestinal diseases or infections), skin rash (cutaneous diseases), or neurological symptoms (neurological or psychiatric diseases).

In a reasonable number of patients, the etiology will remain unclear until all relevant laboratory parameters have been collected. Importantly, acute serum tryptase levels are not known to increase in conditions unrelated to MCA. And, as mentioned, it is also important to recognize that elevated basal serum tryptase levels may be detected in several different conditions (even in healthy individuals) and thus an elevated basal tryptase level alone is not diagnostic of MCA or MCAS.

SUMMARY AND FUTURE PERSPECTIVES

MCAS is a well-defined condition that occurs primarily in patients with IgE-dependent allergies and/or mastocytosis, but may also occur in a number of other conditions. In few cases, no underlying cause or disease will be found, leading to the diagnosis of idiopathic MCAS. Diagnostic MCAS criteria include typical clinical symptoms, often with hypotension, an event-related, substantial increase in serum tryptase levels, and response of clinical symptoms to MC-stabilizing drugs or drugs counteracting the effects of MC-derived mediators. When patients with suspected MCAS are referred, it is helpful to follow a diagnostic algorithm that is able to help differentiate between true MCAS, other MCA-related disorders, and unrelated conditions in which MCs are not involved. A key diagnostic checkpoint is vascular instability (hypotension) combined with other typical signs of MCA, which is almost always seen in MCAS. In the next step, serum tryptase levels are measured. When the event-related increase in tryptase, compared with baseline levels recorded in symptom-free intervals, exceeds a certain threshold (20% from baseline + 2 ng/mL), the diagnosis of MCAS is quite likely. It is also standard to measure other MC-related parameters such as urinary histamine and/or PGD\textsubscript{2} metabolites. However, a selective increase in these mediators (in the absence of an increase in tryptase) may be more frequently associated with chronic MCA or a less severe form of MCA but not with MCAS. In a next step, the response of the symptoms to MC-stabilizing and/or anti-mediator-type drugs confirms the presence of MCAS. In a final phase, the patient is examined for the presence of underlying disorders, such as mastocytosis and IgE-dependent allergy. In this final phase, the MCAS is classified into primary MCAS, secondary MCAS, and idiopathic MCAS.

The algorithm provided in this article is designed to assist in the evaluation and management of patients with suspected MCA and MCAS. In addition, our proposed algorithm should support the preparation and conduct of clinical studies on MCAS.

REFERENCES


Ferrer M, Nuñez-Córdoba JM, Luquin E, Grattan CE, de la Borbolla JM, Sanz ML, et al. Serum total tryptase levels are increased in patients with active lesions associated with insect-induced anaphylaxis shows unique features versus other indolent SM. J Allergy Clin Immunol 2014;133:520-8.


### TABLE E1. Differential diagnoses for patients with elevated basal serum tryptase levels

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Most likely cellular origin of tryptase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
<td>Clonal MCs</td>
</tr>
<tr>
<td>Myelomastocytic leukemia</td>
<td>Myeloblasts, neoplastic MCs</td>
</tr>
<tr>
<td>Ph+ chronic myeloid leukemia</td>
<td>Clonal (immature) basophils</td>
</tr>
<tr>
<td>Chronic basophilic leukemia</td>
<td>Clonal (immature) basophils</td>
</tr>
<tr>
<td>Acute basophilic leukemia</td>
<td>Clonal (immature) basophils</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Myeloblasts</td>
</tr>
<tr>
<td>Myelodyplastic syndrome (MDS)</td>
<td>Myeloblasts, basophils, MCs</td>
</tr>
<tr>
<td>Myeloproliferative neoplasm (MPN)</td>
<td>Myeloblasts, basophils, MCs</td>
</tr>
<tr>
<td>MPN/MDS overlap neoplasm</td>
<td>Myeloblasts, basophils, or MCs</td>
</tr>
<tr>
<td>FIP1L1/PDGFRA+ chronic eosinophilic leukemia</td>
<td>Clonal MCs</td>
</tr>
<tr>
<td><strong>Reactive causes/conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Allergic diseases</td>
<td>MCs</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>MCs</td>
</tr>
<tr>
<td>Chronic inflammatory diseases</td>
<td>MCs</td>
</tr>
<tr>
<td>Chronic helminth infection</td>
<td>MCs</td>
</tr>
<tr>
<td><strong>Other conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Familial alpha-tryptasemia</td>
<td>MCs, other cells?</td>
</tr>
<tr>
<td>Severe kidney disease (renal failure)</td>
<td>MCs</td>
</tr>
<tr>
<td>Normal healthy individual†</td>
<td>MCs</td>
</tr>
<tr>
<td>False-positive test result†</td>
<td>—</td>
</tr>
</tbody>
</table>

* Diseases within this category will often be accompanied by serum tryptase levels within the normal range.  
†Occasional normal healthy individuals may have an elevated basal serum tryptase level in the absence of known causes of an elevated tryptase level and where the basis for the elevation is yet to be determined.  
‡A false-positive test result has been regarded as related to the presence of heterophilic antibodies in previous times. The new version of the tryptase test is considered to avoid this analytical problem. False-positive assays in urine for histamine and its metabolites can be the result of bacterial contamination or diet.