Original Article

# Low Prevalence of Idiopathic Mast Cell Activation Syndrome Among 703 Patients With Suspected Mast Cell Disorders

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***What is already known about this topic?*** Idiopathic mast cell activation syndrome (iMCAS) is characterized by severe, systemic, and recurrent symptoms of mast cell activation with nonclonal etiologies. Studies indicating the prevalence of iMCAS using evidence-based diagnostic criteria are lacking.

***What does this article add to our knowledge?*** Our findings indicate that iMCAS is an uncommon condition among patients suspected of having mast cell disorders. However, its prevalence was higher (27%) in patients with unprovoked anaphylaxis in the current cohort.

***How does this study impact current management guidelines?*** Anaphylaxis appears to be the archetype of MCAS. For diagnosing iMCAS, it is crucial to screen suspected patients using the three diagnostic criteria, perform the blood detection of D816V mutation, and apply recommended diagnostic algorithms.

**BACKGROUND: Idiopathic mast cell activation syndrome (iMCAS) is characterized by severe, episodic systemic mast cell (MC) activation and mediator-related symptoms, an event-related increase in serum tryptase levels, and response to MC-targeted therapies in the absence of underlying IgE-mediated allergy or clonal MC disorder. Studies indicating its prevalence using evidence-based diagnostic criteria are lacking.**
**OBJECTIVE: To assess the prevalence and clinical and laboratory features of patients with iMCAS.**
**METHODS: We conducted a retrospective evaluation of data from 703 consecutive patients (aged ≥18 years) referred to our center based on suspicion of having MC disorders. Patients underwent a thorough clinical workup including patient history, allergy tests, *KIT* D816V mutation analysis, and/or bone marrow investigation. Disease activity was prospectively assessed during follow-up visits.**
**RESULTS: We identified 31 patients with confirmed iMCAS. Furthermore, hereditary α-tryptasemia was detected in three patients with baseline tryptase levels greater than 8 ng/mL. The most common clinical presentation during MCAS episodes was mucocutaneous symptoms in patients with iMCAS, especially urticaria or angioedema. However, these symptoms were less prevalent in patients with clonal MCAS ($P = .015$). The duration of diagnostic delay was significantly longer in patients with iMCAS compared to those with clonal MCAS ($P = .02$).**
**CONCLUSIONS: The overall prevalence of iMCAS was 4.4% in the entire cohort, which indicates that iMCAS is an uncommon condition. To accurately diagnose iMCAS, it is crucial to evaluate suspected patients using the three diagnostic MCAS criteria. This involves performing a comprehensive allergy work-up including laboratory tests and ultrasensitive mutation analysis of *KIT* D816V. Subsequently, recommended diagnostic**

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*Abbreviations used*
*BM- bone marrow*
*cMCAS- Clonal mast cell activation syndrome*
*HαT- Hereditary α-tryptasemia*
*IA- Idiopathic anaphylaxis*
*iMCAS- Idiopathic mast cell activation syndrome*
*MCAS- Mast cell activation syndrome*
*NICAS- National Institute of Health Idiopathic Clonal Anaphylaxis Score*
*PPV- Positive predictive value*
*REMA- Red Española de Mastocitosis (Spanish Mastocytosis on Network)*
*sBT- Serum baseline tryptase*

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***Key words:*** *MCAS; Idiopathic; Anaphylaxis; Mastocytosis; KIT D816V; Hereditary α-Tryptasemia; Mast cell mediator-release symptom; Tryptase*

## INTRODUCTION

Mast cell activation syndrome (MCAS) is a heterogenous rare disorder with few epidemiologic data.[1-3] It is characterized by systemic mast cell (MC) activation with clonal or nonclonal etiologies resulting in severe, recurrent, and episodic symptoms owing to inappropriate MC mediator release.[1-4] An MCAS diagnosis is rendered when three sets of criteria are fulfilled: (1) typical episodic symptoms consistent with systemic MC activation with concurrent involvement of at least two organ systems including cutaneous, gastrointestinal, respiratory, and cardiovascular; (2) objective laboratory evidence that indicates MC activation (ie, an event-related increase in serum tryptase levels according to a formula of 1.2 × baseline tryptase levels + 2 ng/mL); and (3) appropriate response to drugs directed against MC activation.[1-3]

After an MCAS diagnosis is confirmed, patients should be classified into one of three variants.[1-3] Primary (ie, clonal) MCAS (cMCAS), characterized by clonally aberrant MCs exhibiting a somatic *KIT* D816V mutation and/or aberrant expression of CD25, is confirmed by bone marrow (BM) examination. Clonal MCAS is seen with monoclonal MC activation syndrome and mastocytosis (systemic and/or cutaneous). Secondary MCAS is characterized by symptoms of systemic MC activation through IgE- or non−IgE mediated mechanisms (eg, drug-, food- or Hymenoptera venom−induced anaphylaxis) without evidence of clonal population of MCs.[1-3] Finally, there are cases with neither clearly identifiable triggers nor signs of clonal MC population. This condition is classified as idiopathic MCAS (iMCAS).[1-3,5] To obtain a final diagnosis of iMCAS, an extracutaneous biopsy, preferably from the BM, may be necessary to rule out the presence of underlying clonally aberrant MCs.[5] Therefore, the diagnosis of iMCAS is usually time-consuming and remains challenging for clinicians because it mimics cardiovascular, cutaneous, gastrointestinal, endocrinologic, or neurologic conditions owing to the overlapping multisystem symptomatology.[1,6] Furthermore, MCAS has been reported in patients with hereditary α-tryptasemia (HαT), an autosomal dominant genetic trait caused by an increased copy-number of the α-tryptase gene *TPSAB1*, resulting in increased baseline serum tryptase levels.[7,8] However, a clear association between HαT and MCAS has not been fully clarified.

Prescreening tools have been developed to identify MCAS patients who have a higher risk of bearing clonally aberrant MCs and who should undergo BM investigation.[9-11] The Spanish Network on Mastocytosis score (REMAs) is a validated tool based on combined clinical and laboratory criteria to predict underlying MC clonality risk in patients presenting with anaphylaxis without typical mastocytosis skin changes.[12,13] The Karolinska score, a later modification of REMA, has been shown to have better sensitivity and specificity in patients with idiopathic anaphylaxis (IA) by applying a lower baseline serum tryptase cutoff value of 11.4 of 20 ng/mL.[10] A third prediction tool was proposed by the National Institute of Health, the National Institute of Health Idiopathic Clonal Anaphylaxis Score (NICAS).[11] The NICAS score integrates peripheral blood *KIT* D816V mutation analysis[14] with a set of clinical variables and demonstrates higher sensitivity and specificity compared with REMA for detecting MC clonality risk in patients with recurrent unprovoked anaphylaxis.[11]

Mast cell activation syndrome has a suggested prevalence of up to 17%; however, patients suspected of having it are rarely assessed for the three diagnostic criteria, and diagnosis is often based on a number of nonspecific symptoms.[15] Furthermore, MCAS and iMCAS are interchangeably used in the literature, and therefore the actual prevalence of MCAS or iMCAS remains unknown. A recent German study[16] reported that 2% of a cohort composed of 100 patients suspected of having iMCAS had a confirmed diagnosis. Thus, it is essential to apply evidence-based MCAS criteria to distinguish iMCAS from mimicking conditions.[1-3]

There is an unmet need to describe the epidemiologic and clinical characteristics of patients with iMCAS. Hence, the current study aimed to evaluate the prevalence and clinical and laboratory features of patients with iMCAS in a large, well-characterized cohort of patients suspected of having MC disorders. Moreover, we performed a comparative analysis between patients with iMCAS and those with cMCAS.

## MATERIALS AND METHODS

### Study population

The Mastocytosis Center Karolinska was established in 2006 at Karolinska University Hospital and receives referrals from throughout Sweden. As of March 31, 2023, 703 consecutive adult patients (aged >18 years) were referred to the center with anaphylaxis and/or suspected MC disorder. All patients underwent a detailed physical examination and diagnostic workup composed of serum baseline tryptase (sBT) levels, *KIT* D816V mutation analysis, and, when justified, flow cytometry and BM histopathology. A diagnosis of mastocytosis was obtained using current World Health Organization criteria.[17,18] An anaphylaxis diagnosis was established in accordance with the National Institute of Allergy and Infectious Diseases clinical criteria.[19] An MCAS was diagnosed using the Vienna consensus criteria.[1-3]

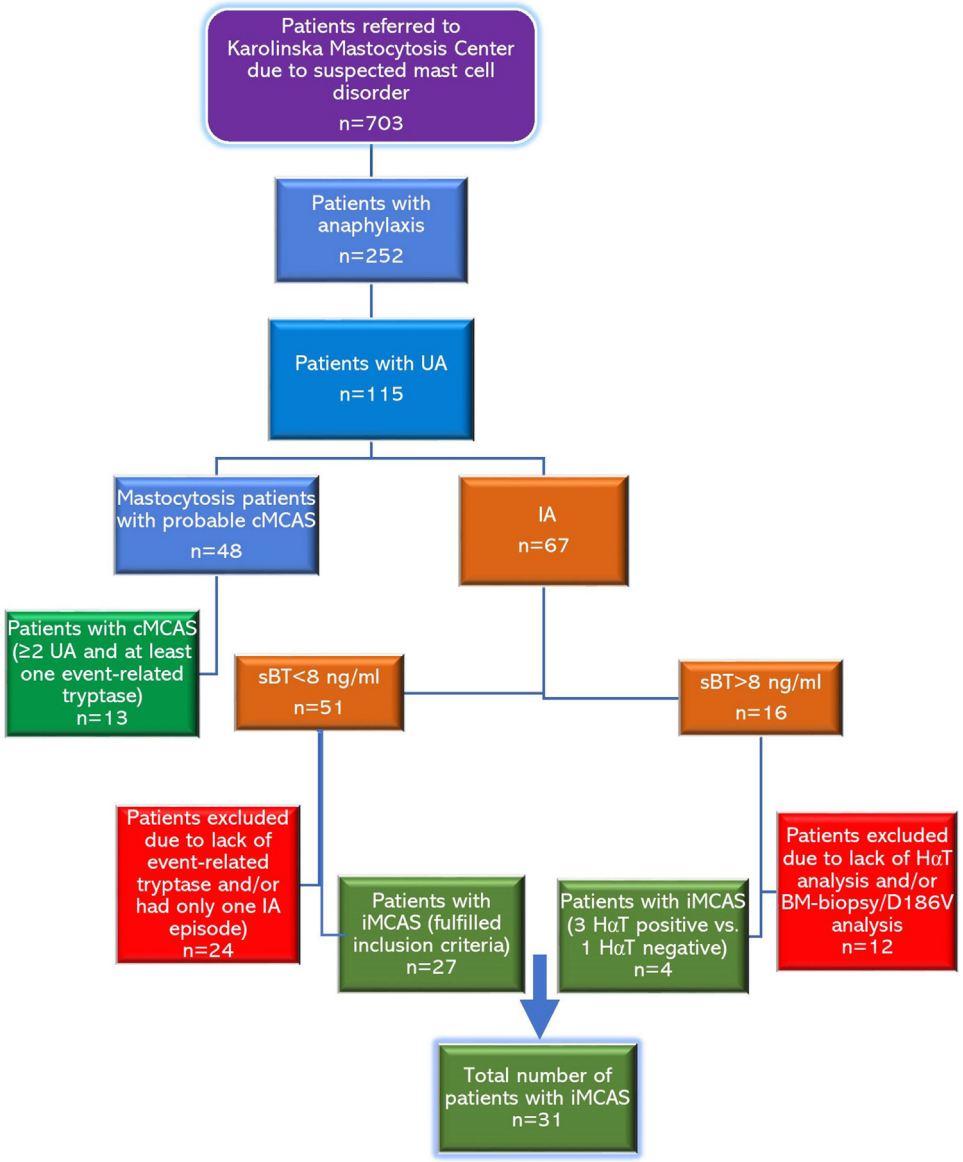


**FIGURE 1.** Flowchart illustrating selection process of patients with confirmed idiopathic mast cell activation syndrome (iMCAS) among nonclonal patients with unprovoked anaphylaxis. *BM*, bone marrow; *cMCAS*, clonal mast cell activation syndrome; *HαT*, hereditary α-tryptasemia; *IA*, idiopathic anaphylaxis; *sBT*, serum baseline tryptase; *UA*, unprovoked anaphylaxis.

## Study design, study subjects, and clinical procedures

We collected data retrospectively from electronic patient records. Figure 1 shows the patient selection process. Of 703 investigated patients, 115 with IA were identified. All patients underwent a comprehensive standardized allergy workup including a detailed medical history and allergy tests such as skin prick test and/or specific IgE antibody test (ImmunoCAP; ThermoFisher, Uppsala, Sweden) to exclude potential triggers including drugs, foods, and venom, to confirm IA. From these, 67 nonclonal patients were identified and reevaluated for iMCAS.

Inclusion criteria were the absence of typical cutaneous lesions of mastocytosis, a history of two or more unprovoked anaphylaxis episodes, a significant increase in event-related tryptase levels at least once, and sBT levels less than 8 ng/mL (to rule out patients with HαT). A negative peripheral blood *KIT* D816V analysis was required for all patients. Patients who fulfilled the first three criteria but had an sBT level greater than 8 ng/mL required both the presence of HαT analysis and a negative D816V analysis and/or a BM biopsy showing no signs of MC clonality. We obtained ethical approval from the Regional Ethical Review Board, Stockholm, Sweden (Approval Nos. 2011/1750-31/3 and 2018/2621-31), and all enrolled patients were informed and gave written consent.

All subjects with iMCAS had negative D816V mutation analysis and/or BM biopsy with the absence of signs of MC clonality, excluding mastocytosis as a possible cause of unprovoked anaphylaxis. In addition, in patients with iMCAS with an sBT greater than 8 ng/mL ($n = 4$), HαT analysis was performed. An HαT diagnosis was made when extra copy numbers of *TPSAB1* gene were detected.

**TABLE I.** Clinical characteristics and clinical course of patients with idiopathic MCAS

| Subject no., sex, and age at diagnosis | Atopy (yes/no), total IgE (kU/L) | Serum baseline tryptase, ng/mL | Acute tryptase | MCAS reaction pattern | MCAS episodes at diagnosis, n | Maintenance therapy | MCAS episodes at follow-up, n | Follow-up after diagnosis, mo | Clinical course | Special comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 1, M, 45 | No, 340 | 3.6 | 10 | SYNC, CARDV, RESP, SKIN | 5 | H1-blockers, antileukotrienes | 1 | 101 | I | BM-px (neg) |
| 2, M, 55 | No, 2,200 | 2.7 | 8.5 | CARDV, RESP, GI, SKIN | 3 | H1-blockers | 1 | 4 | I | BM-px (neg) |
| 3, F, 45 | Yes, 650 | 4 | 10 | CARDV, GI, SKIN | 2 | H1-blockers, antileukotrienes | 2 | 122 | I* | D816V neg |
| 4, F, 33 | No, 30 | 3.9 | 12 | SYNC, CARDV, GI, SKIN | 10 | H1-blockers | 7 | 117 | I* | BM-px (neg) |
| 5, M, 68 | Yes, 850 | 5.4 | 45 | SYNC, CARDV, SKIN | 3 | H1-blockers | 0 | 5 | R | BM-px (neg) |
| 6, F, 59 | No, 30 | 4.9 | 11 | GI, SKIN | 1 | H1-blockers | 0 | 9 | R | D816V neg |
| 7, M, 23 | Yes, 310 | 3.3 | 6.6 | SYNC, CARDV, SKIN | 2 | H1-blockers | 0 | 106 | R | D816V neg |
| 8, M, 42 | No, 32 | 6 | 11 | SKIN, GI | 2 | H1-blockers, antileukotrienes | 0 | 92 | R | D816V neg |
| 9, F, 25 | No, 36 | 2.8 | 18 | SYNC, CARDV, GI, SKIN | 2 | H1-blockers, antileukotrienes, cromolyn sodium | 0 | 91 | R | D816V neg |
| 10, M, 51 | Yes, 85 | 3.1 | 8.8 | SYNC, CARDV, GI, SKIN | 2 | H1-blockers | 0 | 90 | R | D816V neg |
| 11, M, 41 | Yes, 67 | 2.8 | 16 | SYNC, CARDV, RESP GI, SKIN | 2 | H1-blockers | 0 | 109 | R | D816V neg |
| 12, M, 73 | No, 220 | 4.5 | 15 | SYNC, CARDV, SKIN | 2 | H1-blockers | 0 | 121 | R | D816V neg |
| 13, F, 54 | Yes, 630 | 7.1 | 15 | SYNC, CARDV, RESP GI, SKIN | 2 | H1-blockers | 1 | 100 | I | D816V neg |
| 14, F, 68 | No, 140 | 3.9 | 27 | CARDV, RESP, GI, SKIN | 5 | H1-blockers | 0 | 31 | R | D816V neg |
| 15, F, 57 | No, 68 | 4.7 | 29 | SYNC, CARDV, GI, SKIN | 3 | H1-blockers | 1 | 113 | I | D816V neg |
| 16, M, 46 | No, 24 | 4 | 8 | GI, SKIN | 3 | H1-blockers | 0 | 66 | R | D816V neg |
| 17, F, 23 | Yes, 1,100 | 6.1 | 21 | RESP, SKIN | 3 | H1-blockers, antileukotrienes, omalizumab | 0 | 36 | R | D816V neg |
| 18, F, 64 | Yes, 77 | 7.0 | 13 | SKIN, GI | 5 | H1-blockers | 1 | 39 | I | D816V neg |
| 19, F, 33 | No, 180 | 1.6 | 8.8 | SYNC, CARDV, GI, SKIN | 3 | H1-blockers, antileukotriene | 1 | 23 | I | D816V neg |
| 20, M, 73 | Yes, 230 | 4.4 | 51 | CARDV, RESP GI, SKIN | 2 | H1-blockers | 0 | 17 | R | D816V neg |
| 21, F, 61 | Yes, not applicable | 5 | 29 | CARDV, RESP | 2 | H1-blockers | 0 | 30 | R | D816V neg |
| 22, F, 34 | Yes, 40 | 6.5 | 22 | CARDV, GI, SKIN | 2 | H1-blockers | 0 | 223 | R | D816V neg |
| 23, F, 19 | Yes, 28 | 6.9 | 14 | SYNC, CARDV, GI, SKIN | 6 | H1-blockers, antileukotriene | 1 | 188 | I | BM-px (neg) |
| 24, M, 57 | No, 150 | 3.9 | 17 | CARDV, GI, SKIN | 3 | H1-blockers, antileukotriene | 1 | 25 | I | D816V neg |
| 25, F, 38 | Yes, 650 | 4.4 | 13 | SYNC, CARDV, GI, SKIN | 2 | H1-blockers | 1 | 4 | I | D816V neg |
| 26, M, 58 | Yes, 1,100 | 7.9 | 16 | RESP, GI, SKIN | 4 | H1-blockers | 0 | 4 | R | D816V neg |
| 27, M, 53 | Yes, 60 | 4.8 | 16 | SYNC, SKIN, GI | 2 | H1-blockers | 0 | 21 | R | D816V neg |
| 28, F, 60 | No, 110 | 14 | 33 | CARDV, SKIN | 2 | H1-blockers | 0 | 122 | R | BM-px (neg) HαT-pos (3α, 2β) |
| 29, M, 68 | No, 65 | 17 | 31 | SYNC, CARDV, GI, SKIN | 3 | H1-blockers, antileukotriene, cromolyn sodium | 2 | 111 | I | BM-px (neg), HαT-pos (3α, 2β) |
| 30, F, 41 | No, 51 | 12 | 24 | CARDV, GI, SKIN | 2 | H1-blockers, cromolyn sodium | 0 | 96 | R | BM-px (neg) HαT-pos (2α, 3β) |
| 31, M, 59 | Yes, 270 | 9.2 | 72 | CARDV, GI, SKIN | 2 | H1-blockers | 0 | 119 | R | D816V neg HαT-neg (1α, 3β) |

Abbreviation: MCAS, mast cell activation syndrome; sBT, serum basal tryptase; HαT, hereditary alpha tryptasemia; I, improved; R, remission; BM-px, bone marrow biopsy; M, male; F, female.
I* considered as improved due to no new reactions during the last 7 years vs 4 years.
*BM-px*, bone marrow biopsy; *CARDV*, cardiovascular; *GI*, gastrointestinal; *HαT*, hereditary α-tryptasemia; *I*, improved; *MCAS*, mast cell activation syndrome; *neg*, negative; *pos*, positive; *R*, remission; *RESP*, respiratory; *sBT*, serum basal tryptase; *SYNC*, syncope.
Improved was considered to be no new reactions during the past 7 yr vs 4 yr.

**TABLE II.** Comparison of clinical and demographic characteristics in patients with idiopathic mast cell activation syndrome versus clonal mast cell activation syndrome

| Total (n = 44; age ≥18 y) | Idiopathic mast cell activation syndrome (n = 31) | Clonal mast cell activation syndrome (n = 13) | *P* |
|---|---|---|---|
| Age at diagnosis, y (median [range]) | 52 (19-73) | 47 (15-61) | .360* |
| Male sex, n (%) | 15 (48.4) | 8 (61.5) | .317† |
| Presence of atopy, n (%) | 16 (52) | 5 (31.25) | .555† |
| Atopic disease n (%) | 8 (25.8) | 4 (30.8) | .418† |
| Baseline tryptase (median [range]) | 4 (2.7-17) | 11.5 (3.1-120) | **<.001*** |
| Total IgE (median [range]) | 125 (24-2,200) | 51 (5.7-1,100) | .168* |
| Total mast cell activation syndrome episodes in all patients (median/patient) | 112 (3) | 51 (4) | .418* |
| Presence of syncope in all mast cell activation syndrome episodes, n (%) | 44 (39) | 23 (45) | .159* |
| Omalizumab in intervention, | 1 (3.2) | 2 (15.4) | .253* |
| Diagnostic delay, y (median [range]) | 4.5 (0.5-25) | 2 (0.25-7) | **.021*** |
| Follow-up, mo (median [range]) | 92 (4-223) | 54 (10-205) | .203* |
| Cumulative follow-up, y | 192.7 | 74.5 | Not applicable |

*$P$ values were calculated using two-tailed Mann-Whitney $U$ test; bold indicates statistical significance ($P < .05$).
†$P$ values were calculated using $\chi^2$or Fisher exact test.

Furthermore, patients with iMCAS (n = 4) with sBT levels greater than 8 ng/mL underwent BM investigation to exclude clonal population of MCs. Four additional patients underwent BM investigation although they had sBT levels less than 8 ng/mL before peripheral blood D816V mutation analysis was performed in the clinic.

Moreover, we prospectively assessed disease activity and response to MC stabilizers and mediator blockers through follow-up visits until July 31, 2023.

### Statistical analysis

We used IBM SPSS Statistics software (version 28.0, SPSS Inc, Chicago, Ill) to perform statistical analysis. $P$ less than .05 was considered statistically significant. Continuous variables were displayed as medians and ranges, and categorical variables as frequencies and percentages. Mann-Whitney $U$ test was used to analyze group differences considering the nonnormal distribution of the data. In addition, we conducted $\chi^2$ or Fisher exact test when suitable to analyze qualitative (ie, categorical) variables. To compare the diagnostic accuracy of each predicting score model, we calculated the sensitivity and specificity and the positive predictive values (PPVs) and negative predictive values.

## RESULTS

### Patient demographics and general characteristics

We identified 31 patients with confirmed iMCAS (Figure 1). Table I lists the baseline characteristics and clinical course of these patients. Sex was relatively equally distributed (48.4% male). Median age at diagnosis was 52 years (range, 19-73 years). Presence of atopy was confirmed in 52% of patients, and atopic diseases such as allergic asthma and rhinoconjunctivitis were present in 25.8%. Furthermore, median levels of total IgE and sBT were 125 kU/L (range, 24-2,200 kU/L) and 4 ng/mL (range, 2.7-17 ng/mL), respectively. Eight patients underwent BM investigation and showed no signs of MC clonality. Moreover, we performed HαT analysis in four subjects because the sBT level exceeded 8 ng/mL; three tested positive for HαT. The overall number of MCAS episodes was 112 (median, 3 episodes/patient; range, 2-17 episodes/patient) in patients with iMCAS, and syncope was the predominating symptom in 39% (Table II). Median follow-up was 92 months (range, 4-223 months) for patients with iMCAS. All patients showed a positive response to MC-targeted treatments (Table I). The most commonly used MC stabilizing agent was H1-blockers, followed by antileukotrienes.

### Comparison of patients with iMCAS and cMCAS

Moreover, 13 of the 48 clonal patients with unprovoked anaphylaxis were concomitantly fulfilled cMCAS diagnosis, and were included as a comparison group (Figure 1). The sBT levels differed significantly between the iMCAS and cMCAS groups ($P < .001$) (Table II). Median time for diagnostic delay was significantly longer in patients with iMCAS compared with those with cMCAS (4.5 and 2 years, respectively; $P = .02$). There were no statistically significant differences between groups with regard to age, sex, IgE levels, and total number of MCAS episodes per patient (Table II). There were more females in the iMCAS group (51.6%) compared with the cMCAS group (38.5%), although the difference was not statistically significant. Despite a shorter median follow-up in the cMCAS group (54 vs 92 months), there was a higher frequency of MCAS episodes per patient and syncope was more commonly observed compared with the iMCAS group. However, these observations were not statistically significant. Omalizumab was used in one patient with iMCAS and two patients with cMCAS, both with a successful response.

### Clinical features of MCAS episodes

Figure 2, *A* illustrates the most common clinical manifestations during MCAS episodes in patients with iMCAS compared with those with cMCAS. Cutaneous symptoms were most prevalent (100%), especially urticaria and angioedema, during iMCAS episodes, followed by gastrointestinal symptoms (73%), whereas hypotension was the most prevalent symptom among patients with cMCAS (92%). The only significant difference between groups was the occurrence of cutaneous symptoms ($P = .009$), in particular urticaria or angioedema ($P = .015$) (Figure 2, *A*). Patients with cMCAS had a greater prevalence of more severe symptoms such as syncope (77% vs 54%),

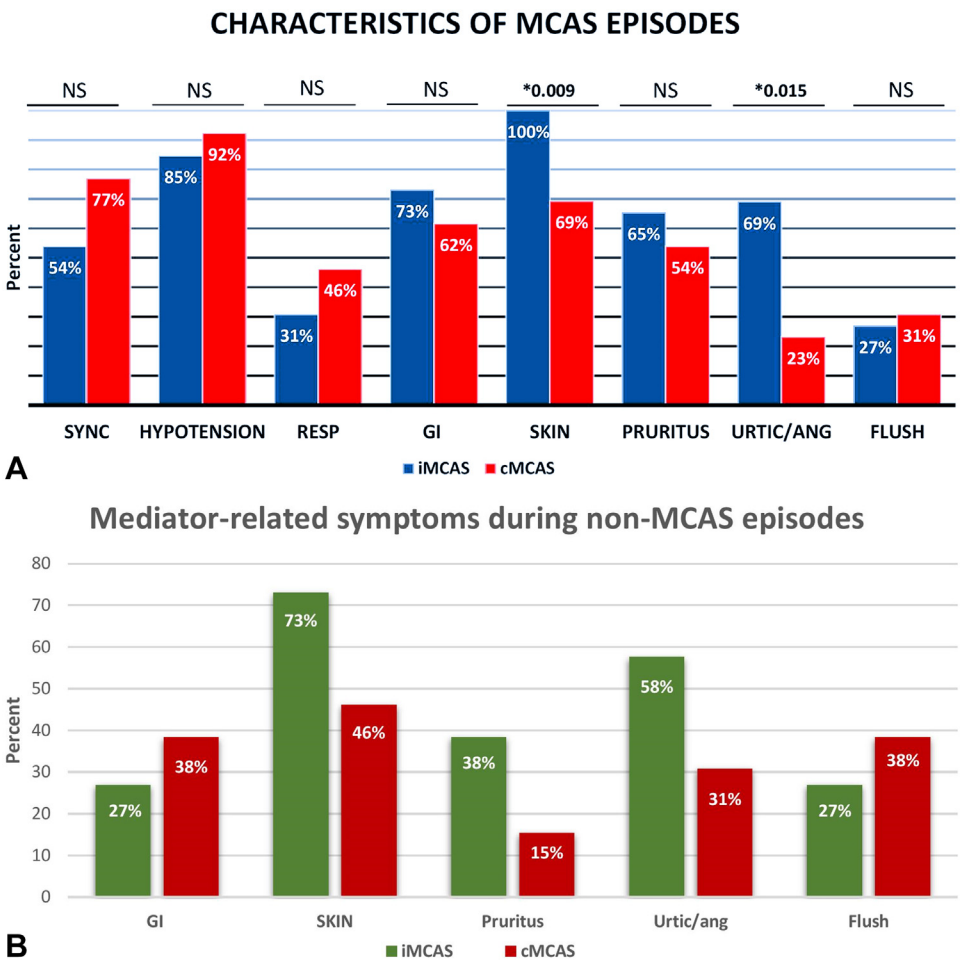


**FIGURE 2.** Clinical characteristics of symptoms. (**A**) Distribution of clinical symptoms during mast cell activation syndrome (MCAS) episodes in patients with idiopathic MCAS (iMCAS) versus clonal MCAS (cMCAS). (**B**) Distribution of less severe mediator-related symptoms during non-MCAS episodes (these symptoms were basically observed at one organ level). *Flush*, flushing; *NS*, nonsignificant; *RESP*, respiratory; *SYNC*, syncope; *Urtik/ang*, urticaria or angioedema. *Statistically significant (Fisher exact test).

hypotension (92% vs 85%), and respiratory symptoms (46% vs 31%), although the differences were not statistically significant.

Figure 2, *B* presents MC mediator-related symptoms with a lower severity than MCAS episodes. Cutaneous symptoms were most common in both groups, with a higher prevalence among patients with iMCAS. Of cutaneous symptoms, urticaria and angioedema were the most prevalent in patients with iMCAS, and flushing was most common in patients with cMCAS (Figure 2, *B*). Gastrointestinal symptoms occurred more commonly in the cMCAS group. These findings were not statistically significant.

## Comparison of clonal MC disorder predicting tools

Three prescreening tools (the REMA, Karolinska, and NICAS) were applied to assess the diagnostic accuracy of detecting underlying MC clonality (Table III). The NICAS score demonstrated the highest accuracy (81%), followed by the Karolinska (71.4%) and REMA (66.7%) scores. The NICAS score was most accurate at ruling out the presence of MC clonality (sensitivity of 92.3% and negative predictive value of 83.3%) compared with the REMA score, the Karolinska score, and the peripheral D816V analysis alone (Tables III and IV). Peripheral D816V analysis as a screening tool, however, had higher accuracy (86%) than the other tools and was the most efficient at detecting the presence of MC clonality (specificity and PPV of 100%) (Table IV).

## Prevalence of MCAS

Of 703 patients with suspected MC disorders, the prevalence of confirmed iMCAS was 4.4% (Table V). In total, 12.3% of patients with anaphylaxis (n = 252) had iMCAS (Table V). In the whole cohort, the prevalence of cMCAS was 1.8%, approximately twofold lower than for iMCAS (4.4%). Among patients with anaphylaxis, 5.2% had cMCAS and the prevalence was approximately the same among patients with clonal MC disorder (n = 254). Not all patients with unprovoked anaphylaxis (n = 115) fulfilled MCAS diagnostic criteria; iMCAS and cMCAS accounted for 27% versus 11.3%, respectively, of patients (Table V). The cumulative prevalence of iMCAS and cMCAS among patients with anaphylaxis was 17.5% (44 of 252). Moreover, the prevalence of patients with suspected iMCAS (ie, lacking one or two diagnostic criteria) was 3.4%.

**TABLE III.** Comparison of clonal mast cell disorder predicting tools applied to both idiopathic mast cell activation syndrome (iMCAS) and clonal mast cell activation syndrome (cMCAS) patients

| iMCAS patients | REMA score | Karolinska score | NICAS | D618V analysis | cMCAS patients | REMA score | Karolinska score | NICAS | D618V analysis |
|---|---|---|---|---|---|---|---|---|---|
| 1* | −1 | −1 | 2 | 0 | 1* | 6 | 6 | 7 | 1 |
| 2* | −1 | −1 | −2 | 0 | 2* | 0 | 0 | 1 | 0 |
| 3 | −6 | −6 | −2 | 0 | 3* | 6 | 6 | 3 | 0 |
| 4* | −3 | −3 | 1 | 0 | 4 | 1 | 3 | 7 | 1 |
| 5* | 2 | 2 | 2 | 0 | 5* | −6 | −6 | 2 | 1 |
| 6 | −6 | −6 | −1 | 0 | 6* | 5 | 5 | 8 | 1 |
| 7 | −1 | −1 | 1 | 0 | 7* | 5 | 5 | 2 | 0 |
| 8 | −1 | −1 | −1 | 0 | 8* | −1 | −1 | 4 | 1 |
| 9 | −3 | −3 | 1 | 0 | 9* | 6 | 6 | 9 | 1 |
| 10 | 2 | 2 | 2 | 0 | 10* | 2 | 2 | 7 | 1 |
| 11 | 2 | 2 | 2 | 0 | 11* | 2 | 3 | 8 | 1 |
| 12 | 2 | 2 | 2 | 0 | 12* | 5 | 5 | 7 | 1 |
| 13 | 0 | 0 | 1 | 0 | 13* | −4 | −4 | 2 | 1 |
| 14 | −3 | −3 | −2 | 0 | | | | | |
| 15 | 0 | 0 | 0 | 0 | | | | | |
| 16 | −4 | −4 | −1 | 0 | | | | | |
| 17 | −6 | −6 | −1 | 0 | | | | | |
| 18 | 3 | 3 | 1 | 0 | | | | | |
| 19 | 0 | 0 | 1 | 0 | | | | | |
| 20 | −1 | −1 | −1 | 0 | | | | | |
| 21 | 0 | 0 | −1 | 0 | | | | | |
| 22 | 0 | 0 | 1 | 0 | | | | | |
| 23* | 0 | 0 | 0 | 0 | | | | | |
| 24 | −4 | −4 | −1 | 0 | | | | | |
| 25 | 0 | 0 | 1 | 0 | | | | | |
| 26 | −4 | −4 | −2 | 0 | | | | | |
| 27 | 3 | 3 | 1 | 0 | | | | | |
| 28* | 0 | 0 | −3 | 0 | | | | | |
| 29* | 3 | 3 | 2 | 0 | | | | | |
| 30* | −3 | −3 | −4 | 0 | | | | | |
| 31 | −3 | −3 | −1 | 0 | | | | | |
| Patients with positive score, n | 7 | 7 | 6 | 0 | Patients with positive score, n | 8 | 9 | 12 | 10 |

*NICAS*, National Institute of Health Idiopathic Clonal Anaphylaxis Score, *REMA*, Red Española de Mastocitosis (Spanish Mastocytosis on Network).
*Patients who underwent bone marrow investigation. Among those eight patients two had a false-positive score for all three tools and one patient had a false-positive score for NICAS only. All patients lacked a positive peripheral blood D816V mutation. Scores are considered positive when they are 2 or greater.

## DISCUSSION

Patients with iMCAS are a heterogenous group poorly characterized in the current literature. Here, we investigated the prevalence and clinical and laboratory characteristics of patients with iMCAS in a large cohort of patients suspected of having mastocytosis. The overall prevalence of iMCAS was 4.4%. The most common clinical manifestation during MCAS episodes was mucocutaneous symptoms in the iMCAS group, especially urticaria or angioedema, which were significantly more prevalent compared with those in patients with cMCAS ($P = .015$). To our knowledge, this is the first study that provides epidemiologic data on patients with iMCAS who received a diagnosis according to the Vienna consensus criteria,[1-3] and which systematically evaluated and compared clinical and laboratory characteristics with those of patients with cMCAS.

There are currently no data on the prevalence of iMCAS in the general population. However, studies report a prevalence ranging from very rare to 17%.[15] Nevertheless, patients in such studies did not fulfil evidence-based criteria of MCAS,[1-3] which makes such reports unsuitable for comparison with our results. In the current study, both iMCAS and cMCAS were relatively uncommon, with a prevalence of 4.4% and 1.8%, respectively. However, this was a special cohort with higher susceptibility to MCAS and a history of anaphylaxis in approximately one-third of patients. Idiopathic MCAS and cMCAS constituted 12.3% versus 5.2% of patients with anaphylaxis (n = 252) in the current study. Another study of patients with suspected iMCAS (n = 100) supports this notion, with a prevalence of confirmed iMCAS of 2%.[16] Thus, the discrepancies in MCAS prevalence across different studies can be explained by the lack of accurate diagnostic criteria during clinical assessment, which leads to misdiagnosis in many cases. Our results may indicate that the actual prevalence of MCAS in the general population is much lower.

Moreover, some patients (n = 24) in the current cohort were classified as having probable iMCAS because they did not satisfy all diagnostic criteria. This resulted from the absence of a confirmed raised tryptase level during episodes or a short follow-

**TABLE IV.** Comparison of diagnostic performance of REMA, Karolinska, and NICAS scores and peripheral blood D816V analysis alone applied to 21 patients investigated with bone marrow biopsy

| Prescreening tool | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) | Accuracy |
|---|---|---|---|---|---|
| REMA | 61.5% (34.8% to 84.1%) | 75% (40.9% to 95.3%) | 80% (50.1% to 96.4%) | 54.5% (26.5% to 80.6%) | 66.7% |
| Karolinska | 69.2% (42.3% to 89.3%) | 75% (40.9% to −95.3%) | 81.8% (53.7% to 96.7%) | 60% (30% to 85.4%) | 71.4% |
| NICAS | 92.3% (70.3% to 99.5%) | 62.5% (29% to 89%) | 80% (56% to 94.6%) | 83.3% (44.6% to 99%) | 81% |
| Peripheral D816V analysis | 76.9% (50.5% to 93.7%) | 100% (NA) | 100% (NA) | 72.7% (43.5% to 92.4%) | 86% |

*NA*, not applicable; *NICAS*, National Institute of Health Idiopathic Clonal Anaphylaxis Score; *REMA*, Red Española de Mastocitosis (Spanish Mastocytosis on Network). Accuracy is defined as the ability to differentiate patients and healthy subjects correctly (ie, the proportion of true negative and true positive results).

**TABLE V.** Prevalence of idiopathic MAS and clonal MCAS in study cohort. *MCAS*, mast cell activation syndrome.

| Characteristics | Idiopathic MCAS (n = 31) | Clonal MCAS (n = 13) | Idiopathic plus clonal MCAS (n = 44) |
|---|---|---|---|
| **Over**all prevalence | 31/703 (4.4%) | 13/703 (1.8%) | 44/703 (6.3%) |
| Of all anaphylaxes | 31/252 (12.3%) | 13/252 (5.2%) | 44/252 (17.5%) |
| Of unprovoked anaphylaxis | 31/115 (27%) | 13/115 (11.3%) | 44/115 (38.2%) |

up, which complicated the evaluation of the MC-targeted therapy response. Those patients were not included. Thus, the overall prevalence in the current cohort might be underestimated. Furthermore, our results show a significantly longer diagnostic delay in patients with iMCAS than in those with cMCAS ($P = .021$). This could be attributed to a longer investigation process before a diagnosis is made, because both primary and secondary MCAS need to be excluded before iMCAS can be established. Patients with iMCAS are not monitored and checked with event-related tryptase levels equally as those with cMCAS, who are known to have MC disorders. Nevertheless, if we compare the diagnostic delay in patients with iMCAS with that in patients with systemic mastocytosis, it was still shorter, because we found a diagnostic delay of 10 years.[20]

Once the diagnostic criteria for MCAS are fulfilled, the disease should be classified according to its specific variant.[1-3] In this context, it is essential to perform a detailed allergy workup, measure sBT levels, and perform ultrasensitive molecular assays to detect *KIT* D816V mutation in the blood. It may also be helpful to apply prescreening scoring tools to select patients who are at risk of underlying clonal MC disease and should undergo a BM biopsy.[9-13] In this study, we found that performing peripheral blood D816V analysis alone had a higher specificity and PPV for predicting MC clonality compared with the three scoring tools. Nevertheless, molecular analysis might yield false-negative results, particularly among patients with a low MC burden or those with *KIT* mutations other than D816V in whom a BM biopsy is required to establish the diagnosis.[21] This emphasizes the need to employ diagnostic algorithms such as REMA, Karolinska, and NICAS among MCAS patients who are suspected of bearing clonally aberrant MCs but have a negative D816V analysis. Consistent with a previous report validating NICAS for IA,[11] the NICAS score showed greater accuracy in excluding and predicting MC clonality compared with REMA in the subjects of the current study, although specificity was lower than REMA. However, this result might be applicable only to patients with recurrent IA. A Spanish study by Rama et al[13] showed that the REMA score exhibited a higher accuracy than the NICAS among patients with anaphylaxis of different etiologies. Hence, the proper use of the REMA versus NICAS might depend on the clinical presentation. In cases for which there is no evidence of IgE-mediated allergy, along with a negative D816V analysis and a score of less than 2 in the REMA, Karolinska, and NICAS tools, a diagnosis of iMCAS is highly probable because the three sets of established criteria of MCAS are fulfilled.

Recently, it was hypothesized that patients with HαT may have an increased susceptibility to MCAS,[7,8] possibly because of higher proteolytic activity promoted by the overexpression of α-tryptase.[22] Moreover, recent studies suggested a close association between MCAS and HαT, with a higher prevalence of HαT carriers among MCAS patients.[13] However, in those studies, no patients fulfilled true MCAS criteria (mostly patients with anaphylaxis). In the current study, we performed HαT analysis on four patients who had sBT levels greater than 8 ng/mL and a negative D816V analysis, and notably three results turned positive. Interestingly, all HαT-positive patients had anaphylaxis episodes affecting the cardiovascular system (hypotension and/or syncope). Despite the paucity of patients involved, this could be because HαT has been shown to be an independent heritable genetic risk factor of severe anaphylaxis.[23] However, further studies are required to understand the true relationship between MCAS and HαT.

Furthermore, we compared demographics, clinical, and laboratory features between patients with iMCAS and those with cMCAS. iMCAS seems to be more likely diagnosed in females compared with patients who have cMCAS, although this was not statistically significant. This may imply a possible underlying genetic or hormonal component in the pathogenesis of iMCAS. In addition, patients with iMCAS presented more frequently with mucocutaneous symptoms compared with patients with cMCAS both during MCAS episodes ($P = .009$) and during episodes that did not reach MCAS severity (not statistically significant, as in shown Figure 2, *B*). Thus, an iMCAS diagnosis is highly suspected for patients who present with mucocutaneous symptoms during anaphylaxis. This is of paramount importance to identify true iMCAS patients, because a high clinical suspicion remains for most patients without iMCAS owing to nonspecific symptoms such as fatigue and musculoskeletal pain.[16]

In contrast, cMCAS patients were more often male and tended to develop more severe MCAS episodes with cardiovascular syncope. These findings are supported by observations in previous studies.[7,24,25] Compared with symptoms in non-MCAS episodes, flushing and gastrointestinal symptoms were more prevalent in

cMCAS, but without statistical significance. This was previously reported for flushing, but not for gastrointestinal symptoms.[10]

A stepwise approach is recommended for treatment options, initially with histamine-receptor blockers, especially type 1.[4,26,27] Most patients in the current study (n = 21) had a favorable response when treated solely with H1 blockers. Omalizumab was shown to be beneficial in a few MCAS patients who were resistant to conventional therapy in this cohort.

The main strength of our study lies in its systematic analysis of iMCAS, using the evidence-based Vienna criteria for diagnosis, which distinguishes it from previous research in this area.[1-3] Furthermore, the comprehensive diagnostic workup, long follow-up, and rigorous inclusion and exclusion criteria made the diagnosis highly reliable. Despite this, our findings are from a single mastocytosis center and may not be generalizable to all patients with iMCAS. Another limitation is the relative paucity of the investigated study subjects, which underscores the need for further research in this area. The exclusion of patients with suspected iMCAS who lacked documented event-related tryptase may have affected the true prevalence of iMCAS in this cohort. Moreover, as previously reported,[16] we focused solely on tryptase as the biomarker for MC activation. Other biomarkers such as prostaglandin $D_2$, leukotriene $E_4$, and N-methylhistamine are relatively less available and less specific and lack defined thresholds.[1,28] However, because tryptase may not be adequately sensitive to detect MC activation in patients with less severe episodes, there is a need for more sensitive markers. Nevertheless, although theoretically feasible, the likelihood of overlooking the diagnosis of such infrequent cases within the current cohort is deemed to be minimal. Finally, we did not screen screening for HαT in iMCAS patients with an sBT less than 8 ng/mL, there is a low possibility of them bearing it because most HαT carriers have an elevated sBT of greater than 8 ng/mL.[1,29,30]

In conclusion, anaphylaxis seems to serve as the archetype for MCAS. Therefore, at the first diagnostic stage, it is essential to determine whether the patient meets criteria for anaphylaxis.[4,5] In this study, we evaluated the prevalence of iMCAS among patients with unprovoked anaphylaxis. Our findings indicate that iMCAS is relatively uncommon. Diagnosing iMCAS is challenging and time-consuming and requires special laboratory and clinical resources that are not always available. For accurately diagnosing iMCAS, it is crucial to screen suspected patients for the three diagnostic criteria of MCAS. This process involves performing a comprehensive clinical workup including a detailed patient history, allergy tests, and ultrasensitive molecular assays of *KIT* D816V, followed by applying recommended diagnostic algorithms (eg, REMA and NICAS). Nevertheless, the relationship between MCAS and HαT requires further investigation, as does the validation of HαT as an eligible genetic biomarker of the increased risk of developing severe recurrent IA and consequently iMCAS. Our study provides a comprehensive characterization of patients with iMCAS, which may contribute to better identification and improved diagnostic precision, as well as the management of these patients.

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