HHS Public Access

Author manuscript

Am J Med Sci. Author manuscript; available in PMC 2018 March 01.

Published in final edited form as:

Am J Med Sci. 2017 March ; 353(3): 207–215. doi:10.1016/j.amjms.2016.12.013.

Characterization of Mast Cell Activation Syndrome

Lawrence B. Afrin, M.D.[1], **Sally Self, M.D.**[2], **Jeremiah Menk, M.S.**[3], and **John Lazarchick, M.D.**[4]

[1]Division of Hematology, Oncology & Transplantation, 420 Delaware St. SE, MMC 480, University of Minnesota (UMN), Minneapolis, MN 55455, afrinl@umn.edu

[2]Department of Pathology and Laboratory Medicine, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, selfs@musc.edu

[3]Clinical and Translational Science Institute (CTSI), University of Minnesota, 717 Delaware St. SE, Room 140-23, Minneapolis, MN 55414, menk0023@umn.edu

[4]Department of Pathology and Laboratory Medicine, Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29425, lazarj@musc.edu

Abstract

Background—Mast cell activation syndrome (MCAS), a recently recognized non-neoplastic mast cell (MC) disease driving chronic multisystem inflammation ± allergy, appears prevalent and thus important. We report the first systematic characterization of a large MCAS population.

Method—Demographics, comorbidities, symptoms, family histories, and physical exam and laboratory findings were reviewed in 298 retrospective and 115 prospective MCAS patients. Blood samples from prospective subjects were examined by flow cytometry for clonal MC disease and tested for cytokines potentially driving the monocytosis frequent in MCAS.

Results—Demographically, white females dominated. Median ages at symptom onset/diagnosis were 9/49 years (ranges 0–88/16–92); median time from symptom onset to diagnosis was 30 years (range 1–85). Median numbers of comorbidities/symptoms/family medical issues were 11/20/4 (ranges 1–66/2–84/0–33). Gastroesophageal reflux, fatigue, and dermatographism were the most common comorbidity, symptom, and exam finding. Abnormalities in routine labs were common and diverse but typically modest. The most useful diagnostic markers were heparin, prostaglandin D_2, histamine, and chromogranin A. Flow cytometric and cytokine assessments were unhelpful.

Corresponding Author: Lawrence B. Afrin, M.D., Division of Hematology, Oncology & Transplantation, University of Minnesota, MMC 480, 420 Delaware Street SE, Minneapolis, MN 55455, afrinl@umn.edu, Telephone: 612-624-0123, Fax: 612-625-6919.

Disclaimer Statement: The authors report they have no conflicts of interest and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship and Conflict-of-Interest Statements

Dr. Afrin was the principal investigator and author and declares no conflicts of interest.

Dr. Self performed and interpreted the flow cytometry studies, reviewed the manuscript, and declares no conflicts of interest.

Mr. Menk performed statistical analyses, reviewed the manuscript, and declares no conflicts of interest.

Dr. Lazarchick performed and interpreted the cytokine analyses, reviewed the manuscript, and declares no conflicts of interest.

Conclusions—Our study highlights MCAS's morbidity burden and challenging heterogeneity. Recognition is important given good survival and treatment prospects.

Keywords

mast cell activation syndrome; mast cell activation disease; chronic inflammatory diseases

Introduction

For the nearly 150 years since discovery of the mast cell (MC) and the first disease associated with the MC (urticaria pigmentosa, the most common form of cutaneous mastocytosis), the spectrum of MC disease has been thought to be comprised principally of rare, neoplastic mastocytosis (both cutaneous (CM) and systemic (SM)) and common, benign, allergic-type phenomena of inappropriate MC activation (e.g., allergy, urticaria, angioedema, anaphylaxis). With recent recognition that inappropriate MC activation is the unifying feature in all MC-driven diseases, there has been both a renaming of the spectrum as "MC activation disease" (MCAD) and new definition of "MC activation syndrome" (MCAS) featuring chronic, inappropriate, non-neoplastic MC activation resulting in multisystem inflammatory ± allergic phenomena not fitting other defined allergic or inflammatory diseases. [1] The role of the MC in allergy has long been widely appreciated, but its many critical roles in inflammation, too [e.g., 2], have perhaps emerged "under the radar." It is becoming increasingly clear that MCAD (the bulk of which is likely MCAS) is a vast collection of diseases featuring different patterns of both aberrant constitutive MC mediator expression and aberrant MC reactivity. It also is becoming increasingly clear that MCs may be activated in both immunologic (e.g., immunoglobulin E-mediated) and non-immunologic (e.g., mediated by cytokines such as corticotropin releasing hormone and substance P) manners. There have been various MCAD classification proposals, some proposing basic categories of primary (clonal), secondary (reactive), and idiopathic [1] and others proposing each case is a relatively unique variant in a complex space (likely driven in most cases by heterogeneous profiles of mutations across many MC regulatory elements (genes, microRNAs, etc. [3])) featuring multiple axes of MC misbehavior including axes of inappropriate activation plus an axis of neoplasticity [4]. Though suggested by preliminary research to possibly be epidemically prevalent [5,6], MCAS is difficult to clinically recognize for many reasons including its novelty, its complex multisystem presentations, and the great heterogeneity of such presentations, this latter aspect thought, again, to be due chiefly to great underlying MC mutational heterogeneity. Although described in various limited fashions in the last decade in case reports (e.g., [7,8]), a patient symptom survey [9], and a few small series (e.g., [10,11]), MCAS has not yet been comprehensively characterized. Presented here is the first systematic objective characterization of a large population of adult MCAS patients.

Methods

The full population of 413 patients studied for this report was comprised of a 298 patient population examined retrospectively (protocol Pro00015852, diagnoses made between November 2008 and September 2012) and a 115 patient population examined prospectively

(protocol Pro00015857, diagnosed made between April 2012 and October 2013) at a single center (the Medical University of South Carolina). Protocols were approved by the center's institutional review board (IRB); the retrospective protocol was deemed IRB-exempt, and all prospective subjects provided written informed consent. Work was funded by a grant from The Mastocytosis Society and by the University of Minnesota Clinical and Translational Science Institute. All diagnoses met published criteria [history consistent with chronic/recurrent aberrant MC mediator release affecting two or more organ systems, absence of any other evident disease (including mastocytosis) better accounting for all symptoms/findings in the case, and at least two elevated levels of mediators relatively specific to MCs (serum tryptase [12], serum chromogranin A (absent confounders of heart or renal failure or recent proton pump inhibitor use or neuroendocrine cancer) [13,14], plasma prostaglandin D_2 [15,16], plasma histamine [12,16], plasma heparin [16,17,18], urinary prostaglandin D_2 [15,16], urinary N-methylhistamine [19,20], urinary leukotriene E4 [21,22], urinary 11-β-prostaglandin-$F_{2\alpha}$ [15,16]) and/or increased MCs identified in extracutaneous tissue] [23] and were made at age 16 or older. For purposes of follow-up, data cut-off was June 30, 2014. Patient demographics, comorbidities, symptoms, and physical exam and laboratory test findings were abstracted by author LBA from the entirety of the subjects' available records. Comorbidities and physical exam findings were all physician-diagnosed; symptoms were all reported by patients either spontaneously or on review of systems. To account for different normal ranges in different assays used over time for any given laboratory parameter, each laboratory test result was normalized with respect to the assay's stated normal range and with an assumption that the normal range encompassed two standard deviations above and below the range's midpoint. Descriptive statistics were used to characterize each examined parameter.

In the prospective population, blood samples were obtained for flow cytometry for established markers, and for serological assessment of putative markers, of MC disease. Flow cytometric studies sought cells co-expressing CD45 and CD117 plus CD25 and/or CD2 [24]; all such studies were performed on a single multicolor flow cytometer and interpreted by a single investigator (SS). To investigate potential drivers of the mild monocytosis frequently seen in MCAS [25], serum levels of monocyte colony stimulating factor (M-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-3 (IL-3), and tumor necrosis factor alpha (TNF-α) – all known key monocyte growth factors and known MC products [14,26,27,28] – were assessed using ELISA kits from RayBiotech, Inc. (Norcross, GA). All assays were performed by a single investigator (JL) per the manufacturer's instructions using kit-provided negative and positive controls.

Results

The majority (69%) of the 413 patients in this study were female; 75% were Caucasian, with virtually all of the rest African-American. Median age at time of self-reported symptom onset was 9 years (range 0–88). Median age at time of diagnosis was 49 years (range 16–92). Median time from symptom onset to diagnosis was 30 years (range 1–85). Median number of comorbidities (problems listed in the medical chart) was 11 (range 1–66). Median number of symptoms reported by patients was 20 (range 2–84). Comorbidities, symptoms, and physical exam findings occurring in at least 10% of the patients are shown in Tables 1,

2, and 3, respectively; all comorbidities, symptoms, and physical exam findings are listed in On-line Supplementary Tables 1, 2, and 3, respectively. Median number of known issues in the family medical history was 4 (range 0–33). Issues occurring in the families of at least 5% of the patients are shown in Table 4; all issues in the family histories are listed in On-line Supplementary Table 4.

Although most of the patients (72%) appeared chronically ill at some point, in general the studied patients appeared healthier than would be expected from their litanies of complaints (e.g., presenting with an objectively normal-for-age extent of hair despite complaint of excessive hair loss), likely contributing to a primary psychiatric diagnosis (especially anxiety, depressive, somatoform, or conversion disorders) experienced by most at one or more points in their extensive prior evaluations. Many patients stated they had “learned to live” with their symptoms and often no longer reported certain symptoms unless specifically asked.

As previously reported for the retrospective subset [25], general laboratory abnormalities in these MCAS patients were common but typically modest in degree (i.e., only slightly above or below the upper or lower limit of normal, respectively) and thus less commanding of attention when viewed as isolated results rather than recurrent findings. Summaries of abnormalities found in routine blood count testing and routine chemistry testing in the entire study population are shown in Table 5. Hematologic abnormalities typically had persisted at least 10 years prior to diagnosis of MCAS; chemistry abnormalities typically had persisted at least 6 years prior to diagnosis.

Summaries of MC mediator levels determined in diagnostic testing are shown in Table 6.

Across the entire prospectively accrued subpopulation, flow cytometric studies (methods detailed in On-line Supplement 5) failed to identify any cells expressing the targeted established signature of clonal MC disease. Also, serum levels of M-CSF, GM-CSF, IL-3, and TNF-α were assessed and, despite finding expected values on negative and positive control samples, were not found elevated in any of the subjects. TNF-α was assessed, once or more, in the clinical lab in 15 of the 413 patients (8 in the retrospective population, 7 in the prospective population) and found elevated at least once in 7 of the 15 patients (47%), including 3 of the prospective subjects. Given our finding of expected results from positive controls, it is unclear why results of our TNF-α assay did not corroborate with the elevated TNF-α levels found in at least these 3 prospective subjects. Different symptomatic states of the disease at time of clinical measurement vs. time of research measurement may have led to these differences in levels.

As of follow-up cut-off, 388 patients (94%) were alive, 1 had been lost to follow-up, and 24 patients (6%) had died of a wide array of causes (N = 1 for each except as noted) including thromboembolism (stroke, pulmonary embolus, anti-phospholipid antibody syndrome), cardiovascular (ventricular tachycardia, heart failure, pulmonary hypertension (2)), infection (septic shock (Plesiomonas shigelloides), aspiration pneumonia and multifocal hemorrhage), other organ failure (refractory ascites, cardiac and hepatic hemosiderosis), cancer (hepatocellular carcinoma, metastatic medullary thyroid carcinoma, angioimmunoblastic T-

cell lymphoma, recurrent metastatic parotid adenocarcinoma, metastatic non-small cell lung cancer, spindle cell pleural neoplasm), or unknown (7). There were insufficient details available regarding these deaths to calculate meaningful statistics regarding survival from time of MCAS diagnosis.

Discussion

In analyses of comorbidities, symptoms, and physical examination findings, this study well demonstrates the principally inflammatory nature of the polymorbidity resulting from MCAS. Comorbidities were defined as diagnoses established in the patients' charts prior to diagnosis of MCAS; although verification of accuracy of these diagnoses was not possible, our data reflect the typically complex nature of patients who come to be diagnosed with MCAS. The multisystemic nature and long duration of symptoms in MCAS highlight the importance of obtaining a complete history in patients with mysterious chronic illness. In particular, it is easy to understand that a long duration of symptoms, together with the historical lack of recognition of MCAS as a potential explanation for such symptoms, can easily lead patients, out of futility, to cease reporting symptoms regardless of severity. Some patients even come to regard such symptoms as within the realm of "normal." One of the authors (LBA) has encountered multiple MCAS patients, for example, who have suffered daily syncope for years and long since stopped reporting such to their physicians after their first few years of such events taught them that death from the symptom was unlikely and no amount of evaluation was likely to provide a diagnosis, much less effective treatment. Only via a thorough review of systems can the clinician gain awareness of such symptoms.

Other interesting associations are seen, too, in these data. Treatment-refractory gastroesophageal reflux disease may reflect undiagnosed MCAS. The preference of MCs for siting themselves not only at environmental interfaces but also at perivascular sites, and the presence of vasoconstriction-driving mediators such as renin amongst the vast MC mediator repertoire [14], begs the question of whether some fraction of the essential hypertension population might be unrecognized MCAS. The author has seen MCAS treatment resolve otherwise refractory hyperlipidemia in some MCAS patients, raising the question of what fraction of the hyperlipidemic population bears MCAS (perhaps with different forms of MCAS driving different forms of hyperlipidemia). The data in this study drive similar questions in the populations with asthma, hypothyroidism, depression, diabetes, fibromyalgia, sleep apnea, idiopathic thromboembolism and idiopathic bleeding/bruising, idiopathic miscarriage, chronic kidney disease, inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, idiopathic headache, idiopathic paresthesias, irritable bowel syndrome and other refractory "functional" abdominal pain, poor healing, inexplicable deterioration of dentition, idiopathic weight gain or loss, insomnia, etc. Patients with unusual or prolific medication reactions, too, may harbor unrecognized MCAS. Neuropsychiatric comorbidities and symptoms, especially anxiety and panic, are common. Interestingly, the benzodiazepine class of medications at the core of treatment of anxiety and panic also addresses inhibitory mast-cell-surface benzodiazepine receptors. [29,30] Physicians (e.g., psychiatrists and emergency physicians) challenged by patients with recurrent idiopathic presentations of anxiety and panic might find more satisfying explanations for these problems in diagnostic assessments for MCAS. Sleep apnea, almost

always obstructive, is found in 15% of MCAS patients and curiously occurs not uncommonly in non-obese patients, raising questions of mechanisms which might include airways narrowed by edema, hypertrophy, fibrosis, or excessive mucus, or excessive loss of airway muscular tone in sleep. Ehlers Danlos Syndrome (EDS) Type III is present in 4% of this cohort, of interest not only because it is the far dominant type of EDS (40% of all EDS cases) but also because it is the only type of EDS for which a specific, highly recurrent mutational cause has not yet been identified. Given that MCs are integrally involved in regulation of growth and development in all tissues, the possibility is raised that some portion of the EDS-III population may bear a particular pattern of chronic MC mediator misexpression being driven by a particular set of mutations in MC regulatory elements. The connective tissue proteins themselves may be normal, but if the ballet of the normal assembly of such proteins into healthy connective tissue is disturbed by chronic incorrect signaling from MCs, healthy connective tissue should not be expected.

As there remains contention regarding diagnostic criteria for MCAS, the recent update to the World Health Organization consensus criteria for diagnosing MC disease makes no statement regarding MCAS. [31] Of the two proposals in the literature for diagnostic criteria for MCAS during the period of our study [23,32], we feel (from experience in >1,000 patients) the Molderings et al. criteria [23] used to identify patients for this study better fit the behavior of the disease. We disfavored the Valent et al. criteria [32] for several reasons discussed previously in the literature [e.g., 33] including (1) nonrecognition of many of the symptoms of MC activation, (2) lack of published validation that the suggested diagnostic tryptase calculation reliably distinguishes ordinary baseline fluctuation of tryptase from fluctuation induced by aberrant MC activation, (3) practical difficulties in providing/obtaining a specimen for serum total tryptase shortly after exacerbation of symptoms, and (4) practical difficulties in finding – in such a heterogeneous disease – effective treatment prior to diagnosis. A slightly modified version of the criteria in [32], allowing wider ranges of MC activation symptoms and markers of MC activation than in [32], was recently proposed. [34]

The frequencies of assorted symptoms in our MCAS cohort were generally consistent with earlier reports in both a general MCAD population (N=420; mastocytosis 75%, MCAS 12%) [9] and a small MCAS population (N=18) [11], underscoring the new understanding that aberrant MC activation, and the symptoms resulting there from, is the unifying feature of most MC disease. In addition to showing the great expanse of inflammatory phenomena in MC disease, data in these three studies highlight the importance of recognizing the differential diagnostic consideration of MC disease in patients with neuropsychiatric symptoms. Differences among the studies (e.g., flushing in 31% of our patients vs. 76% in the patients in [9]) may be due to different methods (e.g., objective exam and chart review in our patients vs. patient self-report in [9]), different definitions (e.g., some facial erythema may have been judged as flush rather than rash), different populations (mastocytosis was dominant in [9] but absent in our cohort and in [11]), and/or other factors. We note, too, that many of the frequencies of various findings in our cohort likely are underestimates given that the majority (72%) of our patients were assessed retrospectively. As such, assessments for specific findings during encounters, and reporting of those assessments in the clinical charts, may not have been performed as rigorously in the retrospective population as in the

prospective population. We expect a more rigorous, exclusively prospective assessment would yield higher frequencies for many, even most, of the parameters shown.

There has been increasing evidence of MC involvement in a variety of chronic inflammatory diseases (CIDs). [e.g., 35,36] For example, 40% of the U.S. population reports gastroesophageal reflux disease (GERD) symptoms [37], and in many the problem is refractory to essentially complete suppression of gastric acid production, suggesting an inflammatory root to this discomfort that is sometimes more specifically diagnostically labeled as non-erosive or functional GERD. Our study adds to suspicions that specific variants of MCAS may underlie fractions of various heretofore idiopathic CIDs. Ultimately, though, proof of such will require, at a minimum, examination of a cohort of patients diagnosed with any given CID to identify not only the proportion of that population in which MCAS (per current diagnostic criteria) is detectable but also the proportion in which such disease is primary, i.e., the proportion in which either MC-activating autoimmunity, or mutations in MC regulatory elements driving constitutive MC activation and/or aberrant MC reactivity, is found. Identification of one or more specific mutational patterns in MCs in patients with any given CID may spur a fundamentally new avenue for investigations into mechanisms and therapeutics for that CID. Of note, even though the hematopoietic origin of MCs assures that mutations found in MCs must be present in (unknown, and likely highly variable) fractions of other types of peripheral blood mononuclear cells (PBMoCs), assessment of the whole PBMoC population for MCAS-driving mutations may be inadequate given that the fraction of the PBMoC population constituted by MCs is so small (0.02%) that mutational “signals” might be lost amidst the background “noise” of normal sequence in the vast majority of PBMoCs (including normal MCs). Until the performance of peripheral blood MC (PBMC) sequencing vs. PBMoC sequencing for detecting MCAS-driving mutations is better understood, prudently designed searches for such mutations should probe both the general unselected PBMoC population and the isolated PBMC population in each subject.

Chronic inflammation is known to be a risk factor for malignancy. The data in this study suggest the families of MCAS patients bear various cancers at much higher rates than the general population, raising the question of whether MCAS underlies significant portions of the populations with at least some types of cancer. The outcome of cancer treatment has long been recognized to improve when comorbid mastocytosis is recognized and concurrently treated. [38] The data in this study suggest it may behoove oncologists to more commonly consider a comorbidity of MCAS when chronic multisystem inflammation and other symptoms more consistent with MC activation than cancer (e.g., syncope in non-metastatic breast cancer) are present in any given cancer patient.

The data in this study show many parameters in “routine labs” are abnormal (e.g., elevations in red cell parameters, monocytes, eosinophils, basophils, transaminases, or alkaline phosphatase), typically to a modest degree, for many years prior to diagnosis of MCAS. (In particular, we note that elevations in eosinophils are seen in many chronic inflammatory diseases in which there have been growing suspicions of critical MC involvement [e.g., 39], raising questions of whether idiopathic eosinophilia by itself might become a useful marker suggesting consideration of MCAS.) Modest laboratory abnormalities unsurprisingly are

given short shrift by busy practitioners when an obvious cause is not apparent, but this study suggests the persistent, or at least frequent, presence of such abnormalities in the context of chronic multisystem inflammation perhaps should spark consideration of MCAS. The chronic presence of such quantitative abnormalities in the MCAS population raises the possibility of developing informatics-based methods by which automated analysis of laboratory results could result in messaging to clinicians providing an initial suggestion of diagnostic consideration of MCAS.

A few specific common laboratory abnormalities deserve further note. A non-trivial fraction of the population (8%) showed JAK2-wild-type polycythemia, observed by author LBA to be associated with likelihood to symptomatically respond to low-dose imatinib ([7,8] and other unpublished data). This finding raises the question of what portion of the roughly 2% of the polycythemia vera population showing wild-type JAK2 might be misrecognized MCAS. Mild microcytosis is common and is typically due to iron deficiency caused either by bleeding or malabsorption secondary to (likely MCAS-driven) duodenal inflammation and/or chronic iatrogenic achlorhydria from proton pump inhibitor therapy addressing chronic gastroesophageal reflux disease. Mild macrocytosis, too, is common, raising the question of what portion of the half of myelodysplastic syndrome cases which are cytogenetically normal might be unrecognized MCAS. Similarly, the commonness of (again, typically mild) thrombocytopenia and thrombocytosis raises the question of what portions of the populations of patients diagnosed, respectively, with autoimmune thrombocytopenia purpura and “triple-negative” (i.e., wild-type JAK2, CALR, and MPL) essential thrombocytosis might harbor unrecognized MCAS.

The relative utilities of various MC mediators tested in diagnostic assessments for MCAS were found in this study (at one institution) to be similar to another large cohort (at a separate institution) recently reported. [40] The present study provides further evidence that plasma heparin is the most useful marker of MC activation, followed closely by prostaglandin D_2 and chromogranin A. Chromogranin A levels, though, can be confounded by heart or renal failure, proton pump inhibitor use, or neuroendocrine cancer. Also, other work has clarified the importance of continuous specimen chilling, including use of refrigerated centrifugation for plasma separation, when seeking plasma heparin levels. [40] Furthermore, our present study adds to evidence mounting in the last decade that the serum tryptase level – while still quite useful as an initial laboratory screen for MC neoplasia in mastocytosis – is a relatively poor indicator of MC activation, and old precepts that MC disease is unlikely when the serum tryptase level is normal can no longer stand. It is clear that mastocytosis is less likely when the serum tryptase level is below the threshold of 20 ng/ml defined in the World Health Organization diagnostic criteria for SM (one study found 30% of indolent SM patients had serum tryptase levels < 20 ng/ml [41]), but there is at least some elevation in tryptase in virtually all SM patients (96% [42]). In contrast, only 62 (16%) of the 388 MCAS patients in this study tested at least once for a serum tryptase level were found to have any elevation in this parameter, and only 15 (24%) of these 62 (or 3.9% of the overall population tested at least once for tryptase) showed at least one serum tryptase level > 20 ng/ml. Tryptase was tested more than once in 88 patients, but in only 2 patients was the tryptase level found > 20 ng/ml more than once. Clearly, serum tryptase at a normal level, or elevated to < 20 ng/ml or perhaps even somewhat above this level, is insufficient to exclude

MCAS. A rise in serum tryptase (over the level determined at an “asymptomatic” baseline, which may not exist) of 20% + 2 ng/ml has been proposed as a discriminator for MCAS [32], but no data supporting this proposal have been published.

Though not specifically designed to examine such, this study hints that survival in MCAS, as already clearly identified in indolent SM [42,43], may be equivalent to that of the general population despite the chronic morbidity of the disease. There are not yet any biomarkers for predicting effective treatments in the individual or for objectively assessing response; symptom self-assessment guides decisions to further pursue vs. cease (at least for a time) trials of yet more of the many therapies shown helpful in various MCAS patients. [44] Formal quality of life assessments are needed, but in the authors’ experience, most patients appear able to eventually identify regimens that help them feel significantly better than their pre-treatment baseline the majority of the time. It is unclear whether diagnosis and treatment of MCAS can reduce the cost of care of these patients.

The negative findings (at least as measured by ELISA) in our exploratory studies offer caution that the few cytokines we were able to assess likely are not integrally involved in production of the intermittent mild monocytosis or thrombocytosis not uncommonly seen in MCAS. As previously noted, the MC’s repertoire of mediators is quite large, and there may be many other mediators which directly or indirectly drive these peripheral blood findings. It may be, too, that other methods of cytokine assessment (e.g., Luminex) might be more productive, perhaps warranting further study of the cytokines we targeted.

Finally, although the racial imbalance in the study population may be a consequence of the single center in which the study was conducted, the gender imbalance in the study population is notable, especially in contrast to a finding of gender balance in most analyses of mastocytosis patient populations. It is unclear whether the imbalance found in this study is a true biological phenomenon, perhaps a consequence of interactions between female sex hormones and their receptors on MCs ± other cells, or whether it is the result of culturally-based bias toward more women than men seeking care for the typically non-life-threatening, non-disabling, non-disfiguring symptoms of MCAS.

In conclusion, MCAS is a recently recognized, likely prevalent and important entity within the realm of MCAD. Its protean manifestation as chronic multisystem polymorbidity of generally inflammatory ± allergic themes hides beneath a cover of extreme heterogeneity of clinical presentation (potentially due to extreme mutational heterogeneity in MC regulatory elements), contributing to significant delays in recognition, diagnosis, and treatment, and yet most MCAS patients, once diagnosed as such, can eventually find significantly helpful treatment. Appreciation by clinicians of the diversity of presentation of MCAS as described in this report may facilitate earlier diagnosis, all the more important given not only good prospects for identifying helpful therapy but also expected long survival in most.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: The Mastocytosis Society; University of Minnesota Clinical and Translational Science Institute.

Research reported in this publication was supported by The Mastocytosis Society and by the National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol. 2010; 126:1099e4–1104e4. [PMID: 21035176]. [PubMed: 21035176]
2. Pejler G, Rönnberg E, Waern I, et al. Mast cell proteases: multifaceted regulators of inflammatory disease. Blood. 2010; 115:4981–4990. [PMID: 20233968]. [PubMed: 20233968]
3. Molderings GJ. Transgenerational transmission of systemic mast cell activation disease -- genetic and epigenetic features. Transl Res. 2016; 174:86–97. [PMID: 26880691]. [PubMed: 26880691]
4. Molderings GJ, Homann J, Raithel M, et al. Toward a global classification of mast cell activation diseases. J Allergy Clin Immunol. 2011; 127:1311. author reply 1311–2 [PMID: 21306766]. [PubMed: 21306766]
5. Haenisch B, Nöthen MM, Molderings GJ. Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. Immunol. 2012; 137:197–205. [PMID: 22957768].
6. Molderings GJ, Haenisch B, Bogdanow M, et al. Familial occurrence of systemic mast cell activation disease. PLoS One. 2013; 8:e76241. [PMID: 24098785]. [PubMed: 24098785]
7. Afrin LB. Polycythemia from mast cell activation syndrome: lessons learned. Am J Med Sci. 2011; 342:44–49. [PMID: 21642812]. [PubMed: 21642812]
8. Afrin LB. Mast cell activation syndrome masquerading as agranulocytosis. Mil Med. 177:113–117. 201; [PMID: 22338992].
9. Jennings S, Russell N, Jennings B, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract. 2014; 2:70–76. [PMID: 24565772]. [PubMed: 24565772]
10. Afrin LB. Burning mouth syndrome and mast cell activation disorder. Oral Surg Oral Med Oral Pathol Oral Radiology Endodontol. 2011; 111:465–472. [PMID: 21420635].
11. Hamilton MJ, Hornick JL, Akin C, et al. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. J Allergy Clin Immunol. 2011; 128:147.e2–152.e2. [PMID: 21621255]. [PubMed: 21621255]
12. Wernersson S, Pejler G. Mast cell secretory granules: armed for battle. Nat Rev Immunol. 2014; 14:478–494. [PMID: 24903914]. [PubMed: 24903914]
13. Prasad P, Yanagihara AA, Small-Howard AL, et al. Secretogranin III directs secretory vesicle biogenesis in mast cells in a manner dependent upon interaction with chromogranin A. J Immunol. 2008; 181:5024–5034. [PMID: 18802106]. [PubMed: 18802106]
14. Ibelgaufts H. “Mast Cells” in COPE: Cytokines and Cells Online Pathfinder Encyclopaedia. 2015 [accessed April 2, 2016] Available at http://www.cells-talk.com/index.php/page/copelibrary?key=mast%20cells.
15. O'Sullivan S. On the role of PGD2 metabolites as markers of mast cell activation in asthma. Acta Physiol Scand Suppl. 1999 Apr.644:1–74. [PMID: 10352758]. [PubMed: 10352758]
16. Dahlén SE, Kumlin M. Monitoring mast cell activation by prostaglandin D2 in vivo. Thorax. 2004; 59(6):453–455. [PMID: 15170020]. [PubMed: 15170020]
17. Seidel H, Molderings GJ, Oldenburg J, et al. Bleeding diathesis in patients with mast cell activation disease. Thromb Haemost. 2011; 106:987–989. [PMID: 21901238]. [PubMed: 21901238]
18. Vysniauskaite M, Hertfelder HJ, Oldenburg J, et al. Determination of plasma heparin level improves identification of systemic mast cell activation disease. PLoS One. 2015 Apr 24.10(4):e0124912. [PMID: 25909362]. [PubMed: 25909362]

19. Keyzer JJ, de Monchy JG, van Doormaal JJ, et al. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983; 309:1603–1605. [PMID: 6646186]. [PubMed: 6646186]
20. Roberts LJ 2nd, Oates JA. Biochemical diagnosis of systemic mast cell disorders. J Invest Dermatol. 1991; 96(3 Suppl):19S–24S. [PMID: 16799604].
21. Raithel M, Zopf Y, Kimpel S, et al. The measurement of leukotrienes in urine as diagnostic option in systemic mastocytosis. J Physiol Pharmacol. 2011; 62:469–472. [PMID: 22100848]. [PubMed: 22100848]
22. Butterfield JH. Increased leukotriene E4 excretion in systemic mastocytosis. Prostaglandins Other Lipid Mediat. 2010; 92:73–76. [PMID: 20380889]. [PubMed: 20380889]
23. Molderings GJ, Brettner S, Homann J, et al. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. J Hematol Oncol. 2011; 4:10. [PMID: 21418662]. [PubMed: 21418662]
24. Escribano L, Díaz-Agustín B, Bellas C, et al. Utility of flow cytometric analysis of mast cells in the diagnosis and classification of adult mastocytosis. Leuk Res. 2001; 25:563–570. [PMID: 11377681]. [PubMed: 11377681]
25. Afrin LB, Wan Z, Hill EG. Characterization of common blood test abnormalities potentially aiding diagnosis of mast cell activation syndrome: a preliminary analysis. Blood. 2013; 122:5240. http://www.bloodjournal.org/content/122/21/5240.
26. Khanna-Gupta, A., Berliner, N. Granulocytopoiesis and Monocytopoiesis. In: Hoffman, R.Benz, EJ.Shattil, SJ.Furie, B.Cohen, HJ.Silberstein, LE., McGlave, P., editors. Hematology: Basic Principles and Practice. 5th. Philadelphia: Churchill Livingstone Elsevier; 2008. p. 303
27. Oster W, Lindemann A, Horn S, et al. Tumor necrosis factor (TNF)-alpha but not TNF-beta induces secretion of colony stimulating factor for macrophages (CSF-1) by human monocytes. Blood. 1987; 70:1700–1703. [PMID: 3499192]. [PubMed: 3499192]
28. Nilsson G, Svensson V, Nilsson K. Constitutive and inducible cytokine mRNA expression in the human mast cell line HMC-1. Scand J Immunol. 1995; 42:76–81. [PMID: 7631148]. [PubMed: 7631148]
29. Hoffmann K, Xifró RA, Hartweg JL, et al. Inhibitory effects of benzodiazepines on the adenosine A(2B) receptor mediated secretion of interleukin-8 in human mast cells. Eur J Pharmacol. 2013; 700:152–158. [PMID: 23266380]. [PubMed: 23266380]
30. Yousefi OS, Wilhelm T, Maschke-Neuß K, et al. The 1,4-benzodiazepine Ro5-4864 (4-chlorodiazepam) suppresses multiple pro-inflammatory mast cell effector functions. Cell Commun Signal. 2013; 11:13. [PMID: 23425659]. [PubMed: 23425659]
31. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19; 127(20):2391–2405. [PMID: 27069254]. [PubMed: 27069254]
32. Valent P, Akin C, Arock M, et al. Definitions, criteria, and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol. 2012; 157:215–225. [PMID: 22041891]. [PubMed: 22041891]
33. Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. World J Hematol. 2014 Feb 6; 3(1):1–17.
34. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med. 2015; 373:163–172. [PMID: 26154789]. [PubMed: 26154789]
35. Pejler G, Rönnberg E, Waern I, et al. Mast cell proteases: multifaceted regulators of inflammatory disease. Blood. 2010; 115:4981–4990. [PMID: 20233968]. [PubMed: 20233968]
36. Afrin LB. Mast cell activation disease and the modern epidemic of chronic inflammatory disease. Transl Res. 2016; 174:33–59. [PMID: 26850903]. [PubMed: 26850903]
37. Cohen E, Bolus R, Khanna D, et al. GERD symptoms in the general population: prevalence and severity versus care-seeking patients. Dig Dis Sci. 2014; 59:2488–2496. [PMID: 24811245]. [PubMed: 24811245]
38. Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. Blood. 2010; 116:5812–5817. [PMID: 20855864]. [PubMed: 20855864]

39. Abonia JP, Blanchard C, Butz BB, et al. Involvement of mast cells in eosinophilic esophagitis. J Allergy Clin Immunol. 2010; 126:140–149. [PMID: 20538331]. [PubMed: 20538331]

40. Zenker N, Afrin LB. Utilities of various mast cell mediators in diagnosing mast cell activation syndrome. Blood. 2015; 126:5174. [accessed March 24, 2016] available at http://www.bloodjournal.org/content/126/23/5194.

41. Sánchez-Muñoz L, Alvarez-Twose I, García-Montero AC, et al. Evaluation of the WHO criteria for the classification of patients with mastocytosis. Mod Pathol. 2011; 24:1157–1168. [PMID: 21552214]. [PubMed: 21552214]

42. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009; 113:5727–5736. [PMID: 19363219]. [PubMed: 19363219]

43. Escribano L, Alvarez-Twose I, Sánchez-Muñoz L, et al. Prognosis in adult indolent systemic mastocytosis: A long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol. 2009; 124:514–521. [PMID: 19541349]. [PubMed: 19541349]

44. Molderings GJ, Haenisch B, Brettner S, et al. Pharmacological treatment options for mast cell activation disease. Naunyn Schmiedebergs Arch Pharmacol. 2016 Jul; 389(7):671–694. [PMID: 27132234]. [PubMed: 27132234]

Key Points

- Mast cell activation syndrome, a prevalent cousin of mastocytosis, may underlie some idiopathic illnesses of inflammatory ± allergic themes.
- Appreciation of the diversity of presentation described here may aid earlier diagnosis and shorten time to helpful therapy for many.

Table 1

Most common (frequency ≥ 10%) comorbidities in mast cell activation syndrome (MCAS).

Comorbidity	Freq.	Comorbidity	Freq.
Gastroesophageal reflux disease	35%	Sleep apnea	15%
Hypertension	29%	Freq. upper resp. infections	15%
Multiple/atypical drug reactions	23%	Miscarriage	15%
Abdominal pain NOS	22%	Pharyngitis and/or tonsillitis	14%
Hysterectomy/oophorectomy	21%	Dysmenorrhea	14%
Hyperlipidemia	20%	Thromboembolism	13%
Cholecystectomy	20%	Freq. and/or atypical infections	13%
Environmental allergies	19%	Obesity	13%
Tobacco abuse	18%	Osteoarthritis	13%
Asthma	18%	Anxiety and/or panic	12%
Diabetes mellitus type 2	17%	Vertebral disease	12%
Hypothyroidism	17%	Cardiovascular malformations	12%
Headaches	17%	Dermatitides	11%
Depression	16%	Presyncope and/or syncope	11%
Sinusitis	16%	Interstitial cystitis	11%
Fibromyalgia	16%	Chronic kidney disease	10%
Anemia of chronic inflammation	15%	POTS	10%

The denominator for each frequency is the eligible portion of the study population (e.g., osteoarthritis: all patients (N = 413); miscarriage: only females (N = 287)).

Abbreviations: NOS – not otherwise specified; POTS – postural orthostatic tachycardia syndrome.

Table 2

Most common (frequency ≥ 10%) symptoms in mast cell activation syndrome (MCAS).

Symptom	Freq.	Symptom	Freq.	Symptom	Freq.
Fatigue	83%	Palpitations/ dysrhythmias	47%	Poor healing	23%
Fibromyalgia-type pain	75%	Sweats	47%	Sinusitis	17%
Presyncope/ syncope	71%	Environmental allergies	40%	Weight gain/obesity	17%
Headache	63%	Fever	40%	Dental deterioration	17%
Pruritus/urticaria	63%	Non-anginal chest pain	40%	Weight loss	16%
Paresthesias	58%	Easy bleeding/ bruising	39%	Cough	16%
Nausea ± vomiting	57%	Alternating diarrhea/constipation	36%	Anxiety/panic	16%
Chills	56%	Proximal dysphagia	35%	Multiple/odd drug reactions	16%
Migratory edema	56%	Insomnia	35%	Dysmenorrhea	16%
Eye irritation	53%	Flushing ± diaphoresis	31%	Asthma	15%
Dyspnea	53%	Visual anomalies	30%	Alopecia	15%
Gastroesophageal reflux	50%	Oral irritation/sores	30%	Constipation	14%
Cognitive dysfunction	49%	Adenopathy/adenitis	28%	Depression	13%
Rashes	49%	Diarrhea	27%	Tremor	13%
Abdominal pain	48%	Urinary sympt. excluding IC	27%	Onychodystrophy	13%
Throat irritation	48%	Frequent or odd infections	27%	Heat and/or cold intolerance	13%

The denominator for each frequency is the eligible portion of the study population (e.g., fatigue: all patients (N = 413); dysmenorrhea: only females (N = 287)).

Abbreviations: IC – interstitial cystitis.

Table 3

Most common (frequency ≥ 10%) physical examination findings in mast cell activation syndrome (MCAS).

Exam Finding	Freq.	Exam Finding	Freq.	Exam Finding	Freq.
Dermatographism	76%	Achy appearance	28%	Pallor	13%
Tired appearance	47%	Bruising	22%	Moderate systolic hypertension (160–179 mm Hg)	12%
Chronically ill appearance	42%	Deterioration of dentition (any type, any extent)	21%	Use of devices to assist mobility	12%
Edema (any degree)	39%	Paresthesia	20%	Cognitive dysfunction (“brain fog”)	12%
Obesity (any degree)	37%	Epigastric tenderness	19%	Flushing	12%
Edema (trace)	35%	LUQ abdominal tenderness	19%	Weakness (global or focal)	12%
Rash (any type)	34%	Edema (more than trace)	16%	Back tenderness (one or more points)	11%
Mild systolic hypertension (140–159 mm Hg)	32%	Soft tissue tenderness	16%	Anxiety	11%
Abdominal Pain (any location, any type, any severity)	32%	RUQ abdominal tenderness	15%	Depressed affect	11%
Tachycardia	28%	Mild diastolic hypertension (90–109 mm Hg)	14%	Cardiac murmur	11%

The denominator for each frequency is the entire study population (N = 413).

Abbreviations: LUQ – left upper quadrant; RUQ – right upper quadrant.

Table 4

Most common medical problems in the families of patients with mast cell activation syndrome (MCAS), extending up to two generations backward and one generation forward and including first and second degree relatives.

Family Medical Problem	Freq.	Family Medical Problem	Freq.
Breast cancer	26%	TIA/CVA	8%
Atherosclerosis	21%	Cancer NOS	8%
Diabetes mellitus type 2	19%	Asthma	7%
Lung cancer	18%	Environmental allergies	7%
Hypertension	17%	Leukemia/MDS	7%
Osteoarthritis	16%	Sickle disease	5%
Rheumatoid arthritis	15%	Head and neck cancer	5%
Colon cancer	15%	Non-Hodgkin lymphoma	5%
Prostate cancer	10%	Brain cancer	5%
Lupus	10%		

Only problems occurring in the families of at least 5% of the patients in this study are shown here; the full listing of medical problems found in the families of this study's patients is shown in On-line Supplementary Table 4.

Abbreviations: CVA – cerebrovascular accident; MDS – myelodysplastic syndrome; TIA – transient ischemic accident.

Table 5

Common abnormalities in routine hematologic and serum chemistry tests found in the study population.

Hematologic Abnormality	Pct.	Hematologic Abnormality	Pct.
RBCs: Anemia (RBC, Hgb, or Hct < LLN)	66%	WBCs: Leukopenia	37%
RBCs: JAK2-w.t. polycythemia (RBC, Hgb, or Hct > ULN)	8%	WBCs: Leukocytosis	45%
RBCs: Microcytosis	24%	WBCs: Monocytosis (relative or absolute)	44%
RBCs: Macrocytosis	29%	WBCs: Eosinophilia (relative or absolute)	40%
RBCs: ↑ mean corpuscular hemoglobin	47%	WBCs: Basophilia (relative or absolute)	25%
RBCs: ↑ mean corpuscular hemoglobin concentration	41%	WBCs: Reactive lymphocytosis	25%
Platelets: Thrombocytopenia	25%	Platelets: Thrombocytosis	25%
Chemistry Abnormality	Pct.	Chemistry Abnormality	Pct.
↑ glucose	75%	↑ ALT	38%
↑ chloride	50%	↓ sodium	35%
↓ albumin	44%	↑ alkaline phosphatase	34%
↓ potassium	41%	↑ creatinine	33%
↑ AST	40%		

The denominator for each frequency is the full cohort of 413 patients.

Abbreviations: ALT – alanine aminotransferase; AST – aspartate aminotransferase; Hgb – hemoglobin; Hct – hematocrit; LLN – lower limit of normal; Pct – percentage of the study population showing the indicated abnormality at least once prior to MCAS diagnosis; RBC – red blood cell count; RBCs – red blood cells; ULN – upper limit of normal; w.t. – wild type; WBCs – white blood cells.

Table 6

Relative utility of assorted mast cell mediators in diagnosing mast cell activation syndrome (MCAS).

Mediator	Min. norm. value	Max. norm. value	Mean norm. value	Median norm. value	Pct. of ↑ tests	Pct. of ↑ pts.	Characterization of elevated results (normalized values)			
							Min.	Max.	Mean	Median
sTryp	−1.50	67.56	0.81	0.02	15%	16%	2.04	67.56	5.77	3.45
sCgA	−1.60	687.36	19.68	1.74	48%	49%	2.04	687.36	41.07	8.07
$pPGD_2$	−2.90	27.40	2.27	1.20	40%	46%	2.05	27.40	5.60	4.05
pHist	−1.78	64.00	2.81	2.00	41%	49%	2.50	64.00	6.05	4.00
pHep	−2.00	32.00	4.66	2.00	45%	48%	4.00	32.00	12.16	12.00
$24uPGD_2$	−3.76	195.07	2.75	1.27	41%	44%	2.02	195.07	7.43	4.78
24uNMH	−2.35	49.93	0.45	−0.02	10%	11%	2.12	49.93	5.77	2.71
$ruPGD_2$	−4.00	36.87	0.65	0.36	22%	26%	2.02	36.87	8.32	5.41
ruNMH	−2.26	6.68	−0.06	−0.28	5%	7%	2.02	6.68	3.28	2.64

As multiple assays, with different normal ranges, were used for each test across the study population (and even within a given patient's chart over time), all values are calculated from normalized test results, assuming each assay's normal range encompassed two standard deviations above and below the range's midpoint; as such, a value < −2 is below the parameter's lower limit of normal, > 2 is above the upper limit of normal, and a value between −2 and 2 is normal.

Abbreviations: Pct. of ↑ pts. – percentage of the study population which underwent at least one test for the indicated parameter and which showed at least one elevated result for that parameter; Pct. of ↑ tests – percentage of testings of the indicated parameter which showed an elevated result; pHep – plasma heparin; pHist – plasma histamine; ruNMH – random urinary *N*-methylhistamine; $ruPGD_2$ – random urinary prostaglandin D_2; sCgA – serum chromogranin A; sTryp – serum tryptase; 24uNMH – 24-hour urinary *N*-methylhistamine; $24uPGD_2$ – 24-hour urinary prostaglandin D_2.