Commentary ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

Small Intestinal Bacterial Overgrowth is Common in Mast Cell Activation Syndrome

Leonard B. Weinstock MD[1], Ali Rezaie MD[2], Jill B. Brook MA[3], Zahid Kaleem MD[4], Lawrence B. Afrin MD[5] and Gerhard J. Molderings MD[6]

[1]*Gastroenterology, Washington University School of Medicine, 11525 Olde Cabin Rd, St. Louis, MO 63141.*

[2]*Gastroenterology, Cedars-Sinai Medical Center, 8730 Alden Dr Ste 204E, Los Angeles, CA 90048.*

[3]*Biostatistics, Private Practice, 13285 Roundhill, Truckee, CA 13285.*

[4]*Pathology, Specialists in Gastroenterology, 11525 Olde Cabin Rd, St. Louis, 63141.*

[5]*Hematology/Oncology, 3010 Westchester Avenue, Suite 401, Armonk, NY 10577.*

[6]*Institute of Human Genetics, University Hospital Bonn, D53127 Bonn, Germany.*

***Correspondence:**

Leonard Weinstock, MD; Gastroenterology, 11525 Olde Cabin Road; St Louis, MO 63141; Telephone: 314-997-0554; Fax: 314-997-5086.

Received: 08 October 2020; **Accepted:** 28 October 2020

Citation: Weinstock LB, Rezaie A, Brook JB, et al. Small Intestinal Bacterial Overgrowth is Common in Mast Cell Activation Syndrome. J Med - Clin Res & Rev. 2020; 4(8): 1-13.

ABSTRACT

Objectives: *Mast cell activation syndrome (MCAS) is a multi-systemic inflammatory and allergic disorder caused by uncontrolled, inappropriate mast cell (MC) activity. Intestinal symptoms in MCAS are common and may mimic irritable bowel syndrome. The latter can be associated with small intestinal bacterial overgrowth (SIBO). The aim was to determine the prevalence of SIBO in MCAS patients with gastrointestinal symptoms.*

Methods: *Patients presenting with refractory intestinal-type symptoms were prospectively evaluated for MCAS and SIBO. MCAS was diagnosed with symptoms of MC activation in ≥2 organ systems plus ≥1 of increased MC mediators, clinical improvement with MC-therapy, and/or increased intestinal MC density. SIBO was defined as a rise of hydrogen rise ≥20 ppm from baseline in a 90 min lactulose breath test and were compared to healthy controls. Impact of co-morbid syndromes and medications were analyzed.*

Results: *Study included 139 patients with MCAS (83.4% female, 46.6 ±16.9 years) and 30 completely healthy controls (63.3% female, 44.0 ±14.0 years). Intestinal symptoms included mid to lower abdominal pain (87.1%), bloating (74.8%), constipation (66.9%), and diarrhea (63.3%). SIBO was present in 30.9% MCAS subjects vs. 10.0% controls (p=0.023). Postural orthostatic tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, MC density, MC mediators, and medications were not associated with breath test changes. Bloating was not associated with breath test results.*

Discussion/Conclusion: *SIBO is common in MCAS but does not explain intestinal symptoms in all patients. Additional disturbances from MC mediators in the gut and the effect of mediators in paraneuronal tissue may play roles.*

Keywords
Mast cell activation syndrome, Small intestinal bacterial overgrowth, Irritable bowel syndrome, Bloating.

Introduction
Mast cell activation syndrome (MCAS) is a common disorder of uncontrolled mast cell (MC) activation with multi-systemic inflammatory and allergic symptoms [1-3]. In a study in Germans, the prevalence of MCAS was estimated to be 17% of the population [4]. In a study of over 400 patients with MCAS, 50% of patients reported symptoms of fatigue, myalgia, conjunctivitis, rhinitis, tinnitus, hives, itching, nausea, heartburn, dyspnea, near syncope, headache, chills, and edema [5]. Virtually all organ systems can be involved in MCAS [6]. MCAS is an often-underdiagnosed complex chronic disorder caused by inappropriate MC release of mediators (which include biogenic amines [e.g., histamine], proteases [e.g., tryptase and chymases], cytokines [e.g., interleukins and TNF-α], eicosanoids [e.g., prostaglandins and leukotrienes], heparin, and growth factors) [7-11]. The aberrant MCs secrete mediators which activate normal MCs which magnifies the clinical disorder.

Intestinal symptoms are commonly reported by these patients and often mistaken by physicians as functional syndromes especially irritable bowel syndrome (IBS) [12]. Local and systemic effects of mediators released by mast cells (MCs) can account for constipation, diarrhea, and pain [13-15]. In a study of biopsy specimens in patients with a clinical diagnosis of IBS-d and IBS-c, histamine and tryptase levels were shown to correlate with pain as were proximity of the MCs to the submucosal nerves [13]. Interestingly, constipation has been linked to deposition of MCs near glial cells and filaments [16]. Thus MC-induced neuropathy may explain reduced peristalsis of the large intestine. A similar mechanism could theoretically affect the small intestine that could lead to small intestinal bacterial overgrowth (SIBO) which can lead to diarrhea [17]. Alternatively, MC mediators could directly activate peristalsis leading to diarrhea.

SIBO is defined as the presence of $>10^3$ colon-forming units per milliliter of jejunal aspirate by culture and is caused by multiple diseases and conditions [18]. The general causes of SIBO are poor motility, anatomical stasis, achlorhydria, maldigestion, and abnormal immunity [18-20]. Recognition of the role of SIBO in intestinal symptoms and syndromes such as IBS is becoming more commonplace [21]. Diagnosis and treatment of the underlying pathophysiology of SIBO can lead to better treatment and reduced relapse of SIBO [17].

The present study determined the prevalence of SIBO in MCAS patients with refractory intestinal symptoms. Multiple clinical variables were studied to see if they had impact on results of the lactulose breath test. This study was exploratory and antibiotic treatment outcomes were not performed.

Methods
From February 2017 through April 2019, consecutive adult patients presenting with refractory intestinal symptoms to a gastroenterologist (LBW) were evaluated for the possible diagnosis of MCAS. All patients diagnosed with MCAS were invited to participate in a study to determine the prevalence of SIBO. The investigation was approved by the Missouri Baptist Medical Center Institutional Review Board in St. Louis, MO (reference #1104) and written informed consent was given by all MCAS patients. When techniques and procedures of the lactulose breath test were established in our digestive disease clinic, we performed a study of completely healthy individuals to determine the false positive rate. This study was approved by the Sterling Institutional Review Board in Atlanta, GA (ID #: 3655-001) and participants gave written informed consent [22]. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. These two institutional review boards were the ethics committees.

MCAS diagnosis was based on criteria established by Molderings et al in 2011 and updated in 2017 [6,23]. The main criteria were presence of typical symptoms of MC activation in 2 or more organ systems. Then one or more minor criteria were required: elevation of MC mediator(s), clinically significant improvement with MC-directed therapy as determined by patient history in follow up clinic visits, and/or intestinal MC density ≥20 per high power field. As opposed to systemic mastocytosis, the bone marrow is normal in MCAS. The degree of clinical improvement in MCAS and gastrointestinal (GI) symptoms was based on reassessment in clinic since there is no validated improvement scale in MCAS. To help confirm a clinical diagnosis of MC activation, the MC mediator release syndrome (MCMRS) questionnaire was given to each subject (Supplement 1) [4]. The MCMRS is a validated questionnaire that assesses the number and severity of symptoms, laboratory, radiographic, and biopsy findings. A score of 9-13 assumes that pathological activation of MCs is assumed as the cause of the complaints. A score ≥14 is considered a clinical confirmation for diagnosis of a MC mediator release syndrome although not MCAS per se. In the current study we used the answers to the MCMRS to support the main criteria for MCAS.

MC mediator measurements were performed in 104 subjects and included: 1) plasma prostaglandin D2 and histamine, 2) serum tryptase and chromogranin A, and 3) 24-hour urine prostaglandin 11-β-PGF2α, N-methylhistamine, and leukotriene E4. In 112 subjects, 8 biopsies were obtained from the second portion of the duodenum (N=108) and/or the terminal ileum (N=16) and were stained with the CD117 immunohistochemical stain. MC density was assessed by a standardized systematic approach where MCs were counted in multiple high-power fields using Nikon BX41 Plan N 40x/0.65 objective magnification. MC density was expressed as a range including <20, 20-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, 91-100, and >100 MC/high power field. The MC density was categorized as follows: 1) diffuse – MC density reported as least common denominator in any of several microscopic fields, 2) focal - highest MC density reported in <3 mutually exclusive microscopic fields. Additional data collection for the patients included: age, gender, height, weight, medications that could affect the breath test results, complete review of systems,

past medical history, and the presence of co-morbid postural orthostatic tachycardia syndrome (POTS) and hypermobile Ehlers Danlos syndrome (hEDS) determined by past history and physical examination. All patients underwent a standard physical examination, orthostatic pulse measurements, and joint flexibility evaluation using the Beighton criteria for hEDS [22].

Exclusion criteria in MCAS subjects included age under 18 years of age, pregnancy, Crohn's disease, ulcerative colitis, and untreated celiac disease. Subjects with fibromyalgia, migraines, headaches, chronic abdominal pain with fatigue, and a previous diagnosis of "IBS" were not excluded since these are amongst the most common problems of MCAS. The subjects who had been diagnosed with "IBS" by previous gastroenterologists all failed to respond to on and off label medical therapy. To help determine if other active GI diseases such as Crohn's and celiac disease were excluded the history and old records were carefully reviewed (LBW). Colonoscopy had been performed in 113/139 (81.3%) and upper endoscopy had been performed in 108/139 (77.7%). Those who had not had a negative biopsy for celiac disease all had negative serology.

The controls were recruited from the staff of the GI department in St. Louis (N=19, females) and their spouses (N=11, males). The females included secretaries, medical technologists, and nurses with equivalent representation. Exclusion criteria in controls included age under 18 years, pregnancy, any GI symptoms, any medical illnesses, prescription medication use, and routine over-the-counter medication use. In order to prevent including subjects in the control group from having a diagnosis of MCAS it was required that any symptoms including allergies and GI symptoms were exclusionary.

Diagnostic criteria for SIBO were determined by the lactulose breath test. Breath samples were collected at baseline and every 15 minutes for 90 minutes after ingestion of 10 g of lactulose mixed in 250 mL of water. Hydrogen and methane content in the samples were analyzed by gas chromatography (QuinTron DP Plus MicroLyzer™, QuinTron Instrument Company, Milwaukee, WI). A positive breath test result was defined as a rise of 20 ppm or more from baseline for either hydrogen, methane, or both gases at or before 90 minutes [23]. A breath test result with methane levels alone ≥10 ppm without a rise of 20 ppm from baseline was defined as excess methane excretion [23]. The use of antibiotics and probiotics were prohibited 4 weeks prior to the breath test. The impact of gender, age, body weight, three concomitant medications (proton pump inhibitors, statins, and thyroid supplements), POTS, hEDS, MC mediator release syndrome score, MC density on the LBT result was analyzed.

The prevalence of a positive SIBO in patients with MCAS was compared to the controls by a Fisher's Exact Test. One-way ANOVA and Chi-squared tests were used to compare subgroups. P-value of 0.05 or less was considered statistically significant. The R 3.5.0 version was used for the statistical software.

Results

There were 139 MCAS subjects (116 F, 23 M, 46.6 ±16.9 years; 83.4% female) and 30 controls (19 F, 11 M, 44 ±14 years; 63.3% female). All subjects diagnosed with MCAS fulfilled the major criteria with multiple symptoms of MC activity with chronic fatigue, muscle pain, headache, tinnitus, rhinitis, and conjunctivitis being amongst the most common systemic symptoms.

Minor criteria evaluation showed: one or more mediator test positive in 74/104 (71.2%) subjects tested and abnormal biopsies in 112 (100%) subjects tested. MC-directed treatment in 139 subjects using twice daily histamine 1 and 2 receptor blockers plus vitamins C (500 mg sustained release) and D (2000 units), quercetin (1000 mg twice daily), and low dose naltrexone (4.5 mg daily) was beneficial in 85.9%, unsuccessful in 7.4%, and the effect at the time of data capture closure was too early to determine in 6.7%. Among MCAS patients, GI symptoms preceded other MCAS symptoms in 66.2%. GI symptoms included abdominal pain (87.1%), bloating (74.8%), constipation (66.9%), diarrhea (63.3%), nausea (61.9%), heartburn (54.0%), and dysphagia (29.5%).

Co-morbid syndromes included POTS in 25.2%, hEDS in 23.7%, and both syndromes in 15.1%. Medications that could potentially affect the breath test included: proton pump inhibitors (23.7%), thyroid supplementation (18.0%), and statins (10.8%).

Gender comparisons showed that more female than male MCAS subjects had diagnoses of POTS (29.6% vs 4.3%, p=0.009), hEDS (27.8% vs 4.3%, p=0.015), and both syndromes (18.3% vs 0%, p=0.024). Females also had higher rates of thyroid supplementation (21.6% vs 0%, p=0.014). No other gender-related differences were found in the subjects.

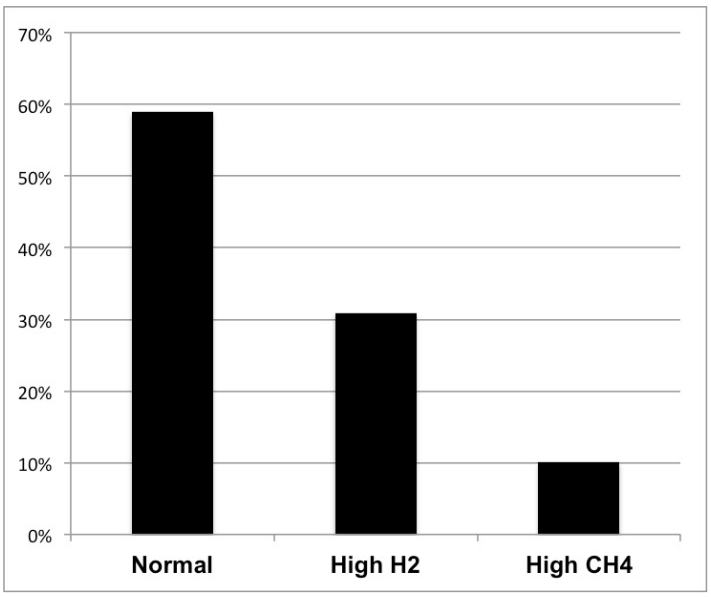


Figure 1: Lactulose breath test results in 139 patients with mast cell activation syndrome.

Forty-one percent of MCAS patients had an abnormal lactulose breath test (Figure 1). Increased hydrogen levels compatible with SIBO were present in 30.9% (43/139) MCAS subjects compared to 10.0% (3/30) controls (p=0.023) (Table 1). Excess methane excretion without a SIBO pattern with levels ≥10 ppm occurred in 10.1% of MCAS subjects and none of the controls. Subjects with constipation predominant bowel habits was associated with excess methane excretion (6/14, 42.9%) as compared to hydrogen-predominant SIBO subjects (4/43, 9.3%, p=0.02; X^2 = 7.91). In subjects with diarrhea predominant bowel habits, 61.1% had elevated abnormal hydrogen levels vs. 33.3% normal levels and 5.6% excess methane excretion (p=0.071). Bloating was not associated with breath test patterns.

Characteristics	MCAS Patients	Controls	P value
Number of subjects	139	30	-
Females	116	19	0.022
Males	23	11	0.022
Age: mean (standard deviation)	46.6 (16.9)	44 (14.0)	Not significant
SIBO (hydrogen) positive: % (count)	30.9 (43/139)	10 (3/30)	0.023

Table 1: Prevalence of small intestinal bacterial overgrowth (SIBO) in mast cell activation syndrome (MCAS) patients and controls.

There was no difference between SIBO positive, SIBO negative, and elevated methane excretion subjects with respect to gender, body mass index, MC mediators, MC density, and MC mediator release syndrome scores, statin use, proton pump inhibitor use, and thyroid supplementation. Prevalence of concomitant POTS, hEDS, or both syndromes was not correlated with breath test results.

Discussion

The novel finding of this study was the high prevalence of abnormal lactulose breath tests in MCAS patients. In the current study, 30.9% of MCAS patients had SIBO as evidenced by an abnormal hydrogen breath testing compared to 10.0% of controls (p=0.023). Our control population had a similar abnormal lactulose breath test rate as reported in the literature [23,24]. In MCAS subjects an additional 10% had elevation of methane levels. There were no underlying co-morbid disorders or medications that had an impact on a SIBO pattern breath test result.

Although IBS had been diagnosed in the majority of the subjects by their former gastroenterologists, there is data to support MC activation as a specific cause for IBS-like symptoms in MCAS patients [7,25-28]. Accordingly, one needs to consider that MCAS may be a causative factor in IBS rather than a coexisting syndrome. MCAS is a common, often underdiagnosed, syndrome that presents to the gastroenterologist as refractory functional GI disorders [3,26]. Identification and specific treatment of this syndrome can lead to a significant improvement in the lives of those affected.

Limitations of this study include the fact that the lactulose breath test is an indirect measure of SIBO and specificity is not ideal [29]. Breath testing, however, is a convenient assessment of bacterial concentration that circumvents problems inherent with invasive intestinal fluid biopsy (i.e., inability to sample the entire small intestine and ineffective culture techniques) [23,30-32]. We do note there is controversy in the literature how best to diagnose MCAS yet we chose the criteria which is more likely to include patients as opposed to excluding them for lack of a history of anaphylaxis and/or rise in tryptase [33,34]. Owing to the clinical nature of this unfunded research project not all subjects had uniform testing (e.g. insurance did not cover and allow for MC mediator testing in 25% of the subjects). Another criticism might include the fact that these patients were diagnosed with MCAS in the setting of the evaluation for refractory intestinal symptoms, yet this scenario is extremely common for the undiagnosed MCAS patient [1-7,29]. Although the specific MC mediators measured in our MCAS subjects did not correlate with a risk for SIBO, this is not unexpected. The MC is capable of producing more than 1000 mediators, but commercial labs are only able to measure a minority, and even fewer are relatively specific to the MC (e.g., tryptase, prostaglandin D2, leukotriene E4, and endogenous heparin) [35]. Mediators also can be secreted locally and not be detectable in the blood or urine. Thus, it could easily be the case that MC mediators responsible for directly or indirectly driving SIBO are not among the mediators measured in the MCAS diagnostic work-up. The inclusion and exclusion criteria for subjects and controls could be criticized. Patients with MCAS were allowed a prior diagnosis of "IBS" and the controls had to be completely healthy. We allowed a prior history of "IBS" because there is evidence that MCAS causes symptoms of IBS and hence MC activation could be the etiology IBS in these cases. We prevented controls from having IBS since they might actually have MCAS. Finally, the value of antibiotic therapy was not analyzed in this study.

In light of the absence of co-factors contributing to SIBO, we hypothesize that MCAS directly contributes to SIBO due to altered motility by local release of MC mediators or alterations of the gastrointestinal immune system. Local autonomic dysfunction could be due to the effects of mediator released by perineuronal mast cells. Another mechanism could be due to damage to interstitial cells of Cajal. A recent study showed that MC deposition was present in achalasia and was associated with a decrease in the interstitial cells of Cajal [36]. Interstitial cells of Cajal in the small intestine are required for initiation and propagation of the intestinal migrating motor complex which is critical in the prevention of bacterial overgrowth. Similar neural involvement by MCs could be present in the small intestine and lead to SIBO. Finally, the direct effect of mediators directly on visceral hypersensitivity and motility could explain symptoms in MCAS patients [27,28].

Conclusion

In this study, SIBO was a common finding in MCAS patients. Establishing the link between SIBO and MCAS provides an additional approach to treat GI symptoms in MCAS patients. Nonetheless there are likely multiple mechanisms to explain GI symptoms in this complex disorder. Additional disturbances from MC mediators in the gut and the effect of mediators in

paraneuronal tissue may play roles in visceral hypersensitivity and bloating. As a corollary, SIBO may activate MC in the mucosa and accordingly reducing SIBO-induced inflammation could reduce GI and extra-intestinal symptoms. Further research is warranted in the mechanisms and treatment of SIBO in MCAS.

Data Availability

The clinical data used to support the findings of this study are included within the supplementary information file.

Supplementary material

1. Mast cell mediator release syndrome questionnaire
2. Clinical data

Conflicts of Interest

Dr. Weinstock and Dr. Rezaie are on the speaker's bureau of Salix Pharmaceuticals. Dr. Rezaie has received research grants and consulting fees from Bausch Health. Dr. Rezaie has equity in Gemelli Biotech. Cedars-Sinai has licensing agreements with Gemelli Biotech. Mrs. Brook does not have any conflicts. Dr. Kaleem does not have any conflicts. Dr. Afrin and Dr. Weinstock are unpaid voluntary medical advisors to the startup company MC Sciences, Ltd. Dr. Molderings is the chief medical officer of the startup company MC Sciences, Ltd.

Funding Statement

Missouri Baptist Medical Center Foundation provided partial support.

References

1. 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: 147-152.
2. Hamilton MJ. Nonclonal mast cell activation syndrome: a growing body of evidence. Immunol Allergy Clin North Am. 2018; 38: 469-481.
3. Hsieh FH. Gastrointestinal involvement in mast cell activation disorders. Immunol Allergy Clin North Am. 2018; 38: 429-441.
4. Molderings GJ, Haenisch B, Bogdanow M, et al. Familial occurrence of systemic mast cell activation disease. PLoS One. 2013; 8: e76241.
5. Afrin LB, Self S, Menk J, et al. Characterization of mast cell activation syndrome. Am J Med Sci. 2017; 353: 207-215.
6. Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. World J Hematol. 2014; 3: 1-17.
7. Afrin LB, Butterfield JH, Raithel M, et al. Often seen rarely recognized mast cell activation disease a guide to diagnosis and therapeutic options. Review article. Ann Med. 2016; 48: 190-201.
8. da Silva EZM, Jamur MC, Oliver C. Mast cell function a new vision of an old cell. J Histochem Cytochem. 2014; 62: 698-738.
9. Vliagoftis H, Befus AD. Mast cells at mucosal frontiers. Curr Mol Med. 2005; 5: 573-589.
10. Albert-Bayo M, Paracuellos I, González-Castro AM, et al. Intestinal Mucosal Mast cell: Key modulators barrier function and homeostasis. Cells. 2019; 8: 135.
11. Rizzi A, Crivellato E, Benagiano V, et al. Mast cells in human digestive tube in normal and pathological conditions. Immunol Lett. 2016; 177: 16-21.
12. Weinstock LB, Rezaie A, Afrin LB. The significance of mast cell activation in the era of precision medicine. Am J Gastroenterol. 2018; 113: 1725-1726.
13. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004; 126: 693-702.
14. Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. Gastroenterology. 2007; 132: 26-37.
15. Wirz S, Molderings GJ. A practical guide for treatment of pain in patients with systemic mast cell activation disease. Pain Physician. 2017; 20: E849-E861.
16. Bassotti G, Villanacci V, Nascimbeni R, et al. Increase of colonic mast cells in obstructed defecation and their relationship with enteric glia. Dig Dis Sci. 2012; 57: 65-71.
17. Rezaie A, Pimentel M, Rao SS. How to Test and Treat Small Intestinal Bacterial Overgrowth an Evidence-Based Approach. Curr Gastroenterol Rep. 2016; 18: 8.
18. Rao SSC, Bhagatwala J. Small Intestinal Bacterial Overgrowth Clinical Features and Therapeutic Management. Clin Transl Gastroenterol. 2019; 10: e00078.
19. Gregg CR, Toskes PP, Feldman M, et al. Enteric bacterial flora and small bowel bacterial overgrowth syndrome. Gastrointestinal and liver disease. 7th ed. Philadelphia. 2002; 2: 1783-1793.
20. Quigley EMM. The Spectrum of Small Intestinal Bacterial Overgrowth SIBO. Curr Gastroenterol Rep. 2019; 21: 3.
21. Giamarellos-Bourboulis EJ, Pyleris E, Barbatzas C, et al. Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage. BMC Gastroenterol. 2016; 16: 67.
22. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. Sleep Med. 2011; 12: 610-613.
23. Molderings GJ, Zienkiewicz T, Homann J, et al. Risk of solid cancer in patients with mast cell activation syndrome Results from Germany and USA. F1000Research. 2017; 6: 1889.
24. Remvig L, Jensen DV, Ward RC. Are diagnostic criteria for general joint hypermobility and benign joint hypermobility syndrome based on reproducible and valid tests. A review of the literature. J Rheumatol. 2007; 34: 798-803.

25. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders the North American Consensus. Am J Gastroenterol. 2017; 112: 775-784.

26. Chen B, Kim JJW, Zhang Y, et al. Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome a systematic review and meta-analysis. J Gastroenterol. 2018; 53: 807-818.

27. Bashashati M, Moossavi S, Cremon C, et al. Colonic immune cells in irritable bowel syndrome A systematic review and meta-analysis. Neurogastroenterol Motil. 2018; 30.

28. Zhang L, Song J, Hou X. Mast cells and irritable bowel syndrome from the bench to the bedside. J Neurogastroenterol Motil. 2016; 22: 181-192.

29. Frieling T, Meis K, Kolck UW, et al. Evidence for mast cell activation in patients with therapy-resistant irritable bowel syndrome. Z Gastroenterol. 2011; 49: 191-194.

30. Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice an evidence-based review of indications and pitfalls in interpretation. Am J Gastroenterol. 2002; 97: 1113-1126.

31. Khoshini R, Dai SC, Lezcano S, et al. A systematic review of diagnostic tests for small intestinal bacterial overgrowth. Dig Dis Sci. 2008; 53: 1443-1454.

32. Saad RJ, Chey WD. Breath testing for small intestinal bacterial overgrowth maximizing test accuracy. Clin Gastroenterol Hepatol. 2014; 12: 1964-1972.

33. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. J Allergy Clin Immunol Pract. 2019; 7: 1125-1133.

34. Afrin LB, Ackerley MB, Bluestein LS, et al. Diagnosis of mast cell activation syndrome: a global consensus-2. Diagnosis. 2020.

35. http://www.CellsTalk.com.

36. Liu ZQ, Chen WF, Wang Y, et al. Mast cell infiltration associated with loss of interstitial cells of Cajal and neuronal degeneration in achalasia. Neurogastroenterol Motil. 2019; 31: e13565.

Mast Cell Mediator Release Syndrome Questionnaire

Patient name _____ Date _____

Age ____ Date of birth _____

Answer all of the following symptoms/questions, even if they are only slightly bothersome, rarely occurring (for instance, not necessary present currently but in the past), or may seem not be related to your main problems. Contact your doctor if you have difficulty completing the questionnaire.

Check (✓) inside the box if the statement applies to you.

If the statement applies to you, enter the intensity level when it was present the last time it occurred on the line next to the box. Please use the range of 1 (very mild) to 10 (unbearable) to reflect the level of your discomfort.

1 2 3 4 5 6 7 8 9 10

CONSTITUTIONAL	**Applies**	**Intensity**
Significant physical weakness or fatigue doing everyday activities	□ **1**	___
Extreme fatigue attacks, so it is hard to keep eyes open	□ **1**	___
At times I lose weight despite maintaining my normal diet	□ **1**	___
Complaints of any type including others below are worsened by:		
Sleep deprivation (awake for more than 24 hours).....	□ **1**	___
Hunger or fasting (no food all day).....	□ **1**	___
High histamine foods (such as red wine, cheese, chocolate, tuna, cured fish/meat, left-over meat)……..	□ **1**	___
Alcohol consumption.....	□ **0**	___
Physical exertion.....	□ **0**	___
Heat.....	□ **0**	___
Cold.....	□ **0**	___
Stress….....	□ **0**	___

EYES/EARS/NOSE/MOUTH
The following occur repeatedly or may be constant:

Ears have ringing or odd sounds and/or	□	___
Eyes are dry, itchy, red, burning, or feel gritty and/or	□	___
Runny nose or stuffy nose and/or	□	___
Inflammation or ulcers of the mouth	□	___
Score 1 if one or more is present .	□ **1**	

CHEST and HEART
The following occur repeatedly or may be constant:

Burning and/or pressure pain in the chest and the heart tests were normal (electrocardiogram and/or stress test)	□ **1**	___
Rapid heart rate (palpitations)	□ **1**	___
Redness or flushing of the skin, especially face or upper body	□ **2**	___

Hot flashes (these usually last 2 to 5 minutes and rarely 10 minutes

and are often accompanied by nausea or other symptoms; these are not hot flashes of menopause) □ **2** ___

Sudden dizziness/lightheadedness with fainting or near faint □ ___
Sudden temporary increase in blood pressure □ ___

Score 2 if one or more is present. □ **2**

I have seen evidence for pulse and blood pressure changes using my digital watch device □

LUNGS
The following occur repeatedly or may be constant:

Irritable dry cough or need to cough and/or □ ___
Feeling of shortness of breath or difficulty taking a full breath and/or □ ___
Asthma-like complaints (wheezing) □ ___
Score 1 if one or more is present. □ **1**

ABDOMEN
The following occur repeatedly or may be constant:
Nausea (with or without vomiting) □ **1** ___
Pain in the abdomen □ **1** ___
Character of pain: burning □ **1** ___
Character of pain: crampy or spastic □ **1** ___
Character of pain: it is associated with diarrhea □ **1** ___

Marked attacks of visible bloating or distension within minutes (up to around 10 minutes) □ **1** ___

A surgeon told me that adhesions (scar tissue) were seen during my very first laparoscopy or abdominal/pelvic surgery □

URINE/PELVIS
The following occur repeatedly or may be constant:

Bladder and/or pelvic pain (this applies to women and men) and is often associated with painful, frequent and/or urgent urination and may be associated with pain during sex. □ **1** ___
During these times bacterial cultures and urine analysis are normal. □
I have had these symptoms but have not seen a doctor to order tests. □

NEUROLOGIC
The following occur repeatedly or may be constant:
Headaches (may be throbbing on one side only or have previously been diagnosed as a migraine) □ **1** ___

Brain fog – word finding problems and/or concentration difficulties with or without associated insomnia episodes. □ **1** ___

Neuropathy: leg pain or arm pain and/or altered feelings (numbness, tingling, pins and needles).
This does not respond to over-the-counter pain medicine. □ **1** ___

SKIN – see last page for photograph examples
The following occur repeatedly or may be constant:

Hives (red raised itchy spots)	□ **1**	___
Itching with or without skin changes	□ **0**	___
Itchy skin lesions that look like acne in the corners of the nasal-lip area, as well as, the chin and forehead during attacks	□ **1**	___
Itching in area around the anus during attacks	□ **1**	___
Painless, non-itchy swelling (especially lips, cheeks, eyelids)	□ **1**	___
Reddish-brown spots and/or knots under the skin	□ **2**	___
Hemangiomas ("blood sponges")	□ **1**	___

HEMATOLOGIC
The following occur repeatedly or may be constant:

Bruising after minor injuries	□	___
and/or		
Unusual nose bleeds	□	___
and/or		
(Women with significantly increased menstrual bleeding)	□	___
Score 1 if one or more is present.	□ **1**	

BONE

Bone pain that usually occurs in more than one bone	□ **1**	
Bone density test showed osteoporosis or osteopenia		
and/or	□	
Whole-body nuclear scintigraphy showed areas of increased bone metabolism without a known cause	□	
Score 1 if one or both is/are present.	□ **1**	

General Questions

Do you get colds regularly which then turn into bacterial infections such as bronchitis or sinus infections?	□ **1**	
Is your illness episodic or comes with attacks?	□ **1**	
Have symptom-free periods become shorter?	□ **1**	
Any degree of relief of nausea by taking antihistamines (examples: diphenhydramine, loratadine, cetirizine)?	□ **1**	
Do you know with relative certainty the beginning of your gastrointestinal and/or other complaints that is linked to a memorable event (infection, stress, environmental change, etc)?	□	

If yes, when and which events? _____
_____

Have your parents, siblings and/or children had similar diseases or syndromes to yours (such as intestinal complaints, food intolerances, pulmonary complaints, allergies, migraine-like headache, pains in various systems without apparent cause, skin changes, hives, itching, runny nose, recurring eye irritation, ringing in the ears, tendency to bruise)? □

List these affected relatives: _____

List of your medications, vitamins, and supplements used regularly or as needed:

_____

_____

_____

_____

Medicine allergies/reactions: _____

_____

Food allergies/reactions: _____

_____

Environmental reactions (odors, temperature, lights, etc.): _____

_____

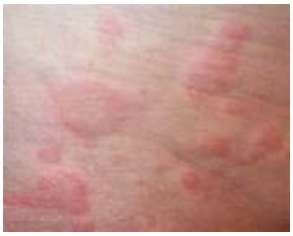
Mold exposure: _____

Tick bite history: _____

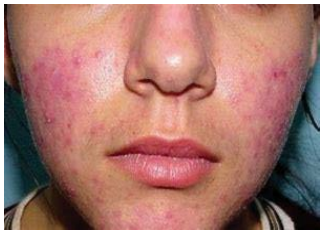
Weight: ____kg (or ____pounds); Height: ____cm (or ___ feet and ___inches)

SKIN PHOTOGRAPHS

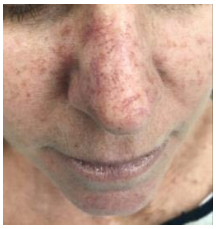
Hives



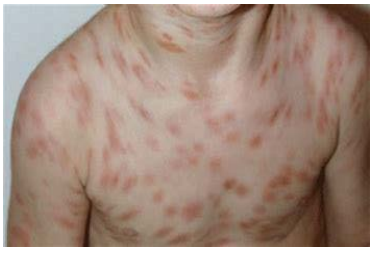
Acne-like lesions



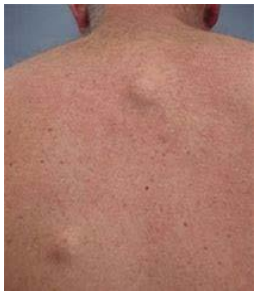
Spider-like veins



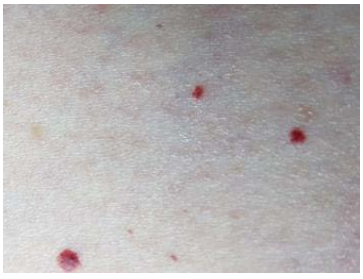
Reddish-brown spots



Knots under skin



Hemangiomas



Laboratory Data

At least once during the disease phases there was:

	Applies
Hyperbilirubinemia up to about 2.5 mg% with the exclusion of Meulengracht/Gilbert's syndrome or another hereditary disorders	□
Increase in transaminases:	
γGT and/or	□
ALT and/or	□
AST and/or	□
Score 1 if one or more is present.	□ **1**
AST increased >10 fold (subtract 1 point and look for other diseases)	□ ***-1***
Hypercholesterolemia (patient must be normal or underweight)	□ **1**
Low titer autoantibodies without a corresponding organ symptom	□ **1**
Mast cell mediators:	
Tryptase in serum was normal	□ **0**
Tryptase was marginally increased	□ **3**
Tryptase increased >2 times the upper limit	□ **10**
Histamine in plasma was normal	□ **0**
Histamine was marginally increased	□ **3**
Histamine increased >2 times the upper limit	□ **10**
Prostaglandin D2 in plasma was normal	□ **0**
Prostaglandin D2 was marginally increased	□ **3**
Prostaglandin D2 increased >2 times the upper limit	□ **10**
Heparin and/or factor VIII in plasma was/were normal	□ **0**
Heparin and/or factor VIII was/were elevated (and bleeding disorders were excluded).	□ **3**
Chromogranin-A in serum was normal	□ **0**
Chromogranin-A was increased (and other causes were excluded)	□ **3**
Leukotriene E-4 in urine was normal	□ **0**
Leukotriene E-4 was marginally increased	□ **1**
Leukotriene E-4 was 10 times the upper limit	□ **5**
Leukotriene E-4 was >10 times the normal limit	□ **10**
N-methylhistamine in urine was normal	□ **0**
N-methylhistamine was marginally increased	□ **1**
N-methylhistamine was 10 times the upper limit	□ **5**
N-methylhistamine was >10 times the normal limit	□ **10**
2,3 Dinor 11b PG F2 alpha in urine was normal	□ **0**
2,3 Dinor 11b PG F2 alpha was marginally increased	□ **1**
2,3 Dinor 11b PG F2 alpha was 10 times the upper limit	□ **5**
2,3 Dinor 11b PG F2 alpha was >10 times the normal limit	□ **10**

Other conspicuous laboratory findings (please name with values) □ **0**

_____

Procedures and Imaging

Esophagogastroduodenoscopy or associated biopsies had:

no pathological findings □ **0**

or

mild inflammation □ **1**

or

Helicobacter pylori-negative and NSAID-negative erosions and/or ulcers □ **3**

or

diffuse and/or focal mast cell infiltrates ≥20/hpf with rounded shape □ **5**

or

Mast cell nests and/or sheets of spindle-shaped mast cells and/or CD25-positive mast cells □ **10**

Colonoscopy and associated biopsies had:

no pathological findings □ **0**

or

mild inflammation □ **1**

or

focal and/or disseminated dense infiltrates of morphologically inconspicuous mast cells □ **5**

or

Mast cell nests and/or sheets of spindle-shaped mast cells and/or CD25-positive mast cells □ **10**

Diseases and disorders below should be excluded in order help confirm the presence of a mast cell disorder. Symptoms in some organ/tissue systems can be similar in both. Evaluate both checklists and the numerical values listed to the right of each box. Add together to get a sum. The data should be entered by the physician.

Sum 9 to 13 = pathological activation of mast cells as cause of complaint is assumed.

Sum ≥14 = diagnosis of mast cell mediator release syndrome is clinically confirmed.

Sum of points: _____ Diagnosis: mast cell mediator release syndrome □

` Differential diagnosis and testing for disorder that may have similar symptoms as mast cell activation

Endocrine disorders

Diabetes mellitus (laboratory determination)
Porphyria (laboratory determination)
Hereditary hyperbilirubinemia (genetic testing)
Thyroid disorders (laboratory determination)
Fabry disease (clinical picture, genetic examination)

Gastrointestinal disorders

Helicobacter-positive gastritis (gastroscopy, biopsy, urea breath test, fecal antigen)
Infectious enteritis (stool examination)
Parasitoses (examination)
Inflammatory bowel disease (endoscopy, biopsy)
Celiac disease (laboratory determination, biopsy)
Lactose, sucrose, or fructose intolerance as an independent disease (history, breath tests)

Microscopic colitis (endoscopy, biopsy)
Amyloidosis (fat biopsy, rectal biopsy)
Adhesions, volvulus, and other intestinal obstructions (history, physical, imaging studies)
Hepatitis (laboratory determination)
Cholecystitis (imaging studies)
Median arcuate ligament syndrome (auscultation, CT angiography with deep expiration views)

Immunological and neoplastic diseases
Carcinoid tumor (laboratory determination, octreotide imaging)
Pheochromocytoma (laboratory determination)
Pancreatic endocrine tumors [gastrinoma, insulinoma, glucagonoma, somatostatin, VIPoma]
(Lab determination, imaging studies, endoscopic ultrasound)
Food allergy/sensitivity (history, special investigations of the biopsies, elimination diet)
Hypereosinophilic syndrome (laboratory determination)
Hereditary angioedema (family history, laboratory determination)
Vasculitis (clinical picture, laboratory value determination)
Intestinal lymphomas (imaging studies)