CASE REPORT

Complex Presentations, Identification and Treatment of Mast Cell Activation Syndrome and Associated Conditions: A Case Report

Alexandra M. Quinn, ND

Abstract

Mast Cell Activation Syndrome (MCAS) is only a recently recognized, multisystem disorder that has been historically underrecognized due its estimated high prevalence. Recognition, testing, and treatment all pose unique challenges to condition management. The condition warrants more concern due to its prevalence and under recognition. Of equal importance in this case is the overlap seen between conditions such as MCAS, gastric dysmotility often manifesting as small intestine bacterial overgrowth (SIBO), dysautonomia, joint hypermobility disorders such as hypermobile Ehlers Danlos Syndrome (h-EDS) or other hypermobility spectrum disorders (HSD), and autoimmunity. This case involves a 42 year-old female who initially presented to the clinic for chronic SIBO and associated gastrointestinal complaints. Upon further examination into the patient's history and unique presentation as visits progressed, important factors affecting treatment considerations were discovered. The patient was ultimately deemed to have other associated conditions including a mast cell-mediated disorder as well as joint hypermobility due to her response to antihistamine and mast cell stabilizing agents. Final outcomes include immense improvement upon mast cell stabilization with ketotifen, and remission of SIBO with low-dose naltrexone (LDN). Although the patient did not undergo testing beyond a serum tryptase test, this case represents the importance of careful history taking and the role of clinical suspicion on patient outcomes.

Alexandra M. Quinn, ND, Northeastern University, Boston, Massachusetts, National University of Natural Medicine (NUNM) Health Centers, Portland, Oregon.

Corresponding author: Alexandra M. Quinn, ND
E-mail address: Alexandra.quinn@nunm.edu

Introduction

A 42 year-old female presented to the clinic with symptoms spanning a multitude of systems. Her past medical history is significant for chronic small intestine bacterial overgrowth (SIBO), not in remission at the time of her first NUNM clinic visit, and thus this was the primary treatment goal when she first visited. The patient had concomitant symptoms that included a 5+ year history of anxiety, fatigue, tachycardia, and palpitations. As the patient's visits progressed, it became apparent that her presentation included another underlying etiology, and thus mast cell-mediated issue was suspected.

Mast cells are part of the innate immune system and after being produced in the bone marrow, migrate to live in connective tissues throughout the body, including vicinity to nerves, blood and lymph vessels, skin, gastrointestinal tract, and the lungs. Acting as sentinels that act as first responders to threats, they quickly mobilize into action and release over 1000 mediators, resulting in inflammation, edema and other allergic-like phenomenon, as well as tissue destruction.[1] When under a perceived stress, mast cells release an inflammatory cascade of mediators and cytokines that, through a number of pathways, leads to CNS inflammation and vascular permeability; the provoking mechanisms can be either IgE-dependent or IgE-independent.[2,3] MCAS is defined as a "chronic, inappropriate, nonneoplastic mast cell activation resulting in multisystem inflammatory and allergic phenomena not fitting other defined allergic or inflammatory diseases."[4] Its prevalence is not fully known, but some suggest that up to 17% of the population may experience it, though due to diagnostic challenges, a recent study showed only 2% of 100 patients reporting MCAS signs and symptoms had elevated serum tryptase blood tests.[5] Etiologies are still being studied but clinical associations have been seen with chronic infections such as mycotoxin illness and Lyme disease, psychological stress, microbiome dysbiosis, trauma and vagal nerve dysfunction, and hypermobility syndromes. There are also increasing connections being made between chemical intolerance (CI) and toxicant-induced loss of tolerance (TILT) as predisposing factors for the development of MCAS due to xenobiotic activation of mast cells in the environment.[1]

Symptoms seen in at least 50% of MCAS patients, in descending order of frequency include: Fatigue, fibromyalgia-type pain, presyncope/syncope, headache, pruritus/urticaria, paresthesias, nausea and/or vomiting, chills, migratory edema, eye irritation, dyspnea, gastroesophageal reflux, cognitive dysfunction, rashes, abdominal pain, throat irritation, palpitations, and sweats. At least 30 other symptoms have been reported with >10% frequency in MCAS patients. Comorbidities seen with >20% frequency, in descending order of occurrence, include: Gastroesophageal reflux disease (GERD), hypertension, atypical drug reactions, abdominal pain NOS, hysterectomy/oophorectomy, hyperlipidemia, cholecystectomy, environmental allergies, hypothyroidism, headaches, depression, type 2 diabetes mellitus, sinusitis, fibromyalgia.[4] At present, two opposing sets of diagnostic criteria exist for the diagnosis of MCAS: Those proposed by Valent, et al. and those by Molderings, et al. The latter proposed criteria accounts for the notorious difficulty in obtaining positive laboratory values that are proposed by Valent: Elevation of at least baseline serum tryptase levels of 20% plus 2 ng/mL and elevations in 24-hour urine levels of other mast cell mediators, including 2,3-dinor-11-beta-PGF2-alpha or *N*-methyl-histamine prostaglandin or histamine metabolite value, and instead focuses on multisystem presentation and response to mast cell and antihistamine therapies.[6,7] A bone marrow biopsy is a major diagnostic criteria of Valent.

H-EDS is a subset of a group of heritable connective tissue disorders termed Ehlers Danlos Syndrome (EDS). Diagnosis of h-EDS, updated in 2017, consists of 3 separate criteria including a Beighton score of at least 5/9 or positive answers to the five-point historical questionnaire. The latter two criteria include an established family history of hypermobility disease and endorsement of skin fragility and exclusion of other heritable and acquired connective tissue disorders.[8] What was once thought to be a purely musculoskeletal disorder has since been recognized to include concomitant "chronic pain, gastrointestinal dysmotility, chronic fatigue, mental manifestations, dysautonomia, and cranial and spinal neurologic complications."[9]

Lastly, though the patient had not received a formal evaluation for dysautonomia, her ongoing tachycardia warrants noting that postural orthostatic tachycardia syndrome (POTS), a subset of dysautonomia characterized by an increase in heart rate of at least 30 beats per minute on standing without concomitant orthostatic hypotension, has a relation to MCAS. There is also a noteworthy prevalence of POTS within the EDS community; in patients with both EDS and POTS, 66% of patients reported mast cell activation symptoms.10 There is also a potential correlation between immune-mediated disorders including MCAS and h-EDS/HSD. Management requires a multifaceted approach that must address the various manifestations of both. No definitive cure currently exists for either condition.

Presenting Concerns

The patient initially presented with concerns of chronic SIBO and associated bloating despite a low FODMAP diet and previous treatments. The patient also had complaints of abdominal pain, muscle spasms, palpitations, brain fog, anxiety, tachycardia, and fatigue, some of which dated back as early as 2015. As the visits progressed, the patient described the occurrence of near-daily "episodes" that began with alternating flushing heat or coldness and clamminess, spasming of the thoracic muscles, a premature ventricular contraction, and ended with violent bursts of diarrhea. The patient also experienced nocturnal urinary frequency, using the restroom every 20 minutes during these episodes. Episodes subsided within 30 minutes by a dose of loratadine. The patient had difficulty identifying specific patterns and triggers of symptom flares but did note that external stimulation in social settings and ingestion of histamine-containing foods, including histamine-ridden leftovers, as contributing factors. The only modifying factors the patient could identify were the use of loratadine and a natural motility supplement containing ginger, which provided the patient symptom relief within 30 minutes.

Clinical Findings

The patient's only diagnosed comorbidities were SIBO verified by a lactulose breath test in 2020, as well as anxiety not managed with pharmaceuticals. The patient's tachycardia and palpitations were previously evaluated with a thorough cardiovascular evaluation, which did not reveal an underlying cause to the patient's cardiac symptoms. Previous treatments included a course of rifaximin for SIBO, as well as current maintenance supplements including multiple herbal prokinetics as a maintenance therapy for prevention of future occurrences, and digestive enzymes, vitamin C, and self-prescribed Claritin.

The patient's other medical and family histories were rather unremarkable; however, upon examination of predisposing factors to mast cell activation and chronic disorders, the patient had notable endorsements of long-term chemical sensitivities to certain fragrances, known mold exposures, joint hypermobility, and a history of trauma, both as a child and an adult. Her physical exams were unremarkable aside from mild diffuse tenderness and responsiveness to visceral hiatal hernia and diaphragmatic release at earlier visits, as well as a positive Beighton score of 7/9. The patient's baseline serum tryptase levels were within normal limits; she did not repeat the test.

Refer to Table 1 in a separate section for timeline of detailed visit summaries and follow-ups.

Diagnostic Assessment

The patient exhibited signs and symptoms of a commonly overlapping group of disorders: Gastric dysmotility (of which SIBO is a subset), joint hypermobility,

Table 1

Dates	Relevant Past Medical History and Interventions
2015	Onset of tachycardia episodes
2017	Onset of patient's wheals, anxiety, and palpitations. Patient had complete cardiovascular evaluation with no abnormalities found
2020	Onset of patient's lethargy/weakness and shooting pain in teeth. Patient presented to a dental clinic, but no etiology was determined
2020	Initial SIBO diagnosis. Treatment course of Rifaximin, low FODMAP diet introduced.
5/16/22	Patient presented to the ED for weakness, with symptoms of brain fog, weakness, nausea of 24 hours' duration. No notable findings.
8/12/22	MyChart notification after patient received acupuncture and two consecutive evenings of symptom flare-ups: While in bed trying to sleep for over 4 hours, patient experienced strong muscle twitching interfering with sleep, feeling a pounding pulse in her face and fingers, feeling flushed, finding she tended to hold her breath instead of breathing normally, and needing to urinate every 20 minutes. She finally took 10 mg Cetirizine and within 20-30 minutes began to noticeably improve. Slept 7 hours but experienced morning grogginess due to the antihistamine

Dates	Summaries from initial & follow-up visits	Assessments//Interventions
7/21/22	The patient presented to the NUNM clinic with complaints of chronic SIBO, anxiety, tachycardia, wheals, palpitations, and fatigue/weakness. Pre-existing medications included 500 mg vitamin C BID, ginger root prn for motility, grapefruit seed extract, Motility Activator by Integrative Therapeutics prn, Atrantil motility supplement prn	2-week 20 mg PO daily omeprazole trial, digestive bitters recommended to patient
8/4/22	Patient's 2nd NUNM visit: Since beginning Omeprazole the patient's physical symptoms of anxiety almost completely subsided. She also reported improved sleep with less frequent nocturia, intense dreams that do not disrupt sleep, and decreased muscle tension. Patient also reported less palpitations and improved heat intolerance. Patient began to experience abdominal cramping and more undigested stool in food, and brain fog, bloating with a cough every 2-3 days remained present. Patient denied sharp abdominal pain but endorsed inability to release gas through belching or flatulence.	Performed a myofascial release of epigastrium and diaphragm, initiated Rifaximin 500 mg TID, recommended digestive enzymes, continuation of digestive bitters
8/16/22	Patient's 3rd NUNM visit: 14-day course of Rifaximin was initiated without subjective response. Patient reported symptoms including muscle spasms, anxiety, palpitations, flushing, abdominal pain, diarrhea, depressed mood, lethargy, nocturnal urinary frequency. Symptoms were all intermittent without recognizable pattern or trigger. Patient self-treated once w/ cetirizine with substantial benefit on 8/11 but discontinued due to next day drowsiness; switched to loratadine once nightly before bed but effectiveness does not match that of cetirizine.	Increased dose of omeprazole to 20 mg PO BID, recommended an increase of loratadine to 1 tablet twice daily and a pause on motility agents until current flare resolved. Continuation of digestive enzymes if preferred.
8/25/22	Patient's 4th NUNM visit: Patient continued to experience the same symptoms. She denied a history of slow motility and hypermobility and wished to start low-dose naltrexone (LDN)	Initiated LDN: Began with 0.5 mg nightly due to patient's sensitivities, gradually tapered up to 4.5 mg nightly
10/13/22	Patient's 6th NUNM visit (first with this case report's author): Patient explained continuance of twice-weekly episodes which included intermittent internal shaking, hot/flushed feeling or a cold/clammy feeling followed by a singular palpitation and bout of diarrhea. Still unsure of what triggers her flares. Ginger root tea and motility pro help acutely but not prophylactically.	Patient advised to continue 4.5 mg daily LDN, introduced compounded ketotifen 1 mg nightly for mast cell stabilization, increased quercetin intake to 500 mg BID Introduction of *Lactobacillus rhamnosus*, a histamine-specific probiotic strain to aid in post-antibiotic gut flora replenishment, limbic system retraining suggested to patient
11/3/22	Patient's 7th NUNM visit: Patient had not yet started her lowered dose of ketotifen (0.25 mg nightly); patient was originally prescribed 1 mg but experienced extreme drowsiness. Patient also expressed interest in tapering off of PPIs as previously discussed and replacing with an H2 antihistamine; had not tried any previously. Only H1 antihistamine patient had not yet tried was fexofenadine	Lowered dose of ketotifen for mast cell stabilization to 0.25 mg nightly, replaced omeprazole with an H2 blocking agent, cimetidine, diaphragmatic release, craniosacral therapy (CST), and visceral abdominal releases performed in-office.
11/9/22	Patient sent MyChart message with a treatment update stating the lowered dose of ketotifen was "wonderful" and that the patient felt better than she had in a couple of years. Patient began to crave high histamine "restricted" foods such as ham and cream cheese and experienced no ill response to them. Patient reported extreme satisfaction with allowance for less strict dietary measures due to ketotifen.	
12/1/22	Patient's 8th NUNM visit: Patient's episodes decreased dramatically in their intensity; frequency remains ~2-3 mild flares/week. Patient no longer experiencing culmination of diarrhea and palpitations. Patient still able to explore new foods into diet without symptoms. SIBO symptoms remain in remission. Patient also began neurofeedback therapy and has experienced profound effects	Recommended to continue with current medication regimen, mycotoxin urine testing suggested.

and mast cell disorders. Diagnostic labs to evaluate for MCAS, as previously mentioned, are notoriously difficult to obtain a diagnosis outside of strong clinical suspicion and response to antihistamine medications. Symptoms primarily manifested in the GI, appeared without pattern or known triggers aside from social stimulation and histamine-containing foods or leftovers, and concluded with episodes of diarrhea. Alternating flushing and clamminess, occasional palpitations, fatigue, tachycardia, and anxiety were also present. No formal diagnosis of h-EDS had been previously made but the patient did endorse extensive family history of hypermobility, and the patient scored 7/9 on Beighton scale on a later office visit. The patient's earlier physical exams revealed diffuse abdominal tenderness and response to diaphragmatic release. Serum tryptase levels were within normal limits; the patient did not obtain a second sample. Despite the lack of additional testing, clinical presentation and clear response to antihistamine medication continued to propel suspicion of a mast cell-related disorder. Other notable features of the patient's presentation included a positive mold questionnaire indicating the likelihood of mycotoxin illness, chemical sensitivities, similarity of symptoms often associated with functional mast cell disorders, as well as an endorsement of trauma and psychological stress as contributing factors to aberrant mast cell release. The patient also exhibited some signs of dysautonomia, a condition associated with MCAS, and further assessment of this could also be of value.

Therapeutic interventions

After a mast cell-mediated disorder was recognized, the patient was treated with a number of modalities that included compounded and over-the-counter medications and supplements.

Quercetin. A bioflavonoid found naturally in foods such as apples, onions, and garlic that exhibits mast cell stabilizing properties in addition to its anti-inflammatory, antiallergenic, anti-cancer, and antioxidant effects. Bioflavonoids belong to a larger group of substances called polyphenols that also include phenolic acids, lignans, and coumarins, which were historically reported as substances other than vitamin C to have effects on capillary fragility. Quercetin has been clinically studied to have an inhibitory effect on mast cell granule release and thus the prevention of proinflammatory compounds.[2] We suggested a dose of 1g daily for this effect.

Vitamin C. Studies have shown the role of vitamin C as a natural antihistamine and antioxidant.[11] Vitamin C is also a preferred therapy for h-EDS patients due to its role in connective tissue synthesis. Suggested doses range from 500-1000 mg daily.

H1 receptor antagonist, fexofenadine. The least sedating of the H1 antagonists and due to the patient's struggle with drowsiness from loratadine despite its effectiveness in abating acute symptoms, fexofenadine was the preferred H1 antihistamine for the patient. A systematic review of the use of H1 blocking agents in MCAS revealed significant improvements in quality of life and symptom control of itching, wheals and flares, flushing, tachycardia, and headache. Due to the lack of H1 receptors in the GI tract, gastrointestinal symptoms were not abated by H1 blockers.[12] Dosage was suggested at 180 mg daily.

H2 receptor antagonist, cimetidine. The suggested use of a histamine-2 receptor blocker instead of omeprazole is due to its preferred safety profile over proton pump inhibitors. Long-term acid suppression by PPIs can lead to hypergastrinemia with the potential of developing gastric cancer, significant vitamin (B12 and C) and mineral (iron, calcium magnesium, and zinc) malabsorption, as well as infections of the urinary tract, respiratory system, and enteric system.[13] Alternatively, H-2 blockers do not predispose patients to hypochlorhydria or other side effects to the same pathologic degree as PPIs. These are especially helpful in the management of GI manifestations of MCAS patients due to the prevalence of H2 receptors in the GI tract. Dosage was suggested at 200 mg daily.

Low-dose naltrexone (LDN). Low-dose naltrexone is a mu-opioid antagonist using pharmacologically low doses (1 to 5 mg). The proposed mechanisms of LDN include acting as a glial modulator, inducing the production of endorphins, and binding to and antagonizing toll-like receptor 4, which eventually produces inflammatory products such as tumor necrosis factor (TNF)-α, interferon-β, interleukin (IL)-1, and nitric oxide.[14] These inflammatory proteins are proposed to activate mast cell activity. Additionally, endorphins are associated with migrating motor complex (MMC) improvement and thus it can be theorized that LDN acts as a mild prokinetic. Opioid antagonists are also proposed to modify gastric motility by stimulating peristalsis and therefore increasing transit time.[15] There are currently no clinical guidelines for the use of LDN. Clinical research to date consists mostly of the use of LDN as a promising treatment for chronic inflammatory pain conditions. Clinical trial abstracts currently show LDN being studied for use in a wide range of immune-mediated conditions, including regional complex pain syndrome, painful diabetic neuropathy, psoriasis, inflammatory bowel disease (IBD), chronic fatigue syndrome, autism, opioid side effects, prevention and treatment of immunothrombosis in Covid-19, relapsing depression, multiple sclerosis (MS), and fibromyalgia. There are currently 62 clinical trials studying LDN in as wide-ranging of conditions.[16,17] The majority of research concerning gastrointestinal conditions is centered around its stimulation of mucosal healing in IBD, though it is often used off-label as a mild prokinetic agent in the management and relapse prevention of SIBO.[14]

Lactobacillus rhamnosus. A probiotic strain for histamine-sensitive individuals. Data suggest that probiotics *L. rhamnosus* Lc705 and *L. rhamnosus* GG specifically could diminish mast-cell activation and the

effects of allergy-related mediators by downregulating expression of the high-affinity IgE and HRH4 receptors, and by stimulating mast-cell immune responses.[18] Dosage was suggested at 1 capsule daily.

Ketotifen. A compounded mast cell stabilizer with additional H2 receptor blocking capabilities that was integral in this patient's treatment outcomes. The agent has been primarily studied for its role in chronic idiopathic pain conditions that are associated with various allergy types.[19] Due to aberrant release of mast cell mediators, stabilization of the mast cells is the first priority when working with a patient with multisystem, connected conditions. Ketotifen completely changed the course of the patient's healing journey and has allowed the patient to return to a state of stability so that underlying triggers could be further assessed. Ketotifen is also preferred for its low toxicity and safety profile compared to other pharmaceutical options. Dosage initially began at 0.25 mg nightly, well under the suggested starting dose of 1 mg BID, due to patient sensitivities, and has been gradually tapered to 0.5 mg nightly with proposed increases by 0.25 mg to the patient's tolerance until a maintenance dose of 1 mg nightly is reached.

Follow-up and Outcomes

The patient was first seen by the medical student and author of this case report after she had already had 5 office visits to the NUNM clinic; a total of 8 visits were made. During her first few visits managed by another medical student, a trial of omeprazole for dyspepsia and rifaximin for SIBO treatment were prescribed. The patient's anxiety responded to the proton pump inhibitor but did not address other GI manifestations. The patient was also prescribed LDN for prevention of a SIBO relapse, to which she responded positively after a gradual dose tapering.

Refer to Table 1 below for timeline specifications of patient follow-up visits and outcomes, which included notable improvement from natural and pharmaceutical antihistamine and mast cell stabilizing agents, as well as improved safety profile of treatment by replacing omeprazole with an H2 receptor antagonist.

Discussion

This case is a notable reminder to look for hidden and underlying similarities and etiologies to patients that present with multisystem complaints. MCAS is a historically underrecognized condition with associated medical literature only recently increasing, and thus when patients experience unexplained symptoms that span at least two systems, it is worthwhile to keep in a differential diagnosis. Beyond the recognition lies the importance of assessing for the presence of associated conditions, including dysautonomia, gastric dysmotility, joint hypermobility, and autoimmunity as a final manifestation of immune dysregulation. Due to the interconnectedness of multisystem conditions, it is imperative to first prioritize mast cell stabilization before addressing other components of a MCAS patient.

The environment poses an increasingly greater threat to human health due to climate change, air pollution, xenobiotics and carcinogens in an omnipresent array of products, and pesticide consumption. As human exposures increase, so has the prevalence of toxicant-induced loss of tolerance (TILT) and chemical sensitivities (CI) in individuals. Environmental triggers are associated with dysfunction beyond aberrant mast cell release, most notably including endocrine disruption. Other widespread environmental concerns, especially in certain climates, include the presence of mold and mycotoxins in living and working quarters. Other chronic infections to assess for include Lyme disease and viruses such as Epstein Barr Virus.

Major strengths of this case included the patient's noteworthy compliance and adherence to the treatment plan. Moreover, the patient also acknowledged the need to address and treat the psychological impacts that trauma can play on health outcomes.[20] Her willingness to participate in modalities such as limbic system retraining and neurofeedback resulted in dramatic changes after only a short period of time. Future considerations will include mycotoxin urine testing followed by an associated treatment protocol if indicated, as well as further addressing vagal tone and the autonomic nervous system.

Patient Perspective

Throughout the visits that were conducted at the NUNM clinic, the patient's primary goals consisted of maintaining SIBO remission and decreasing the frequency and intensity of mast cell episodes so she could begin "feeling like herself" again after nearly two years of unexplained illness. As she regained increasing stability through the use of both over-the-counter and compounded medications as well as natural supplements, the patient became more invested in identifying and addressing underlying causes to her condition to avoid the long-term use of polypharmacy to manage her symptoms. Due to these motivating factors, the patient has been interested in exploring a wide array of therapeutic modalities and etiologies to her condition, which in only a short period of time has already resulted in dramatic improvements.

Due to these motivating factors, the patient has been interested in exploring a wide array of therapeutic modalities and etiologies to her condition. After the submission of this case report, she continued to be seen throughout the remainder of the academic year, during which she was tested and treated for substantial mycotoxin illness as a major influence on her MCAS. Treating mycotoxicity in patients with Mast Cell Activation Syndrome requires patience and heavy therapeutic modifications due to extreme sensitivity. As of June 2023, the patient's symptoms have remained stable amidst the addition of these additional treatment protocols.

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