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CASE REPORT | SMALL BOWEL

Imatinib and Trigger Avoidance for Mast Cell Activation Syndrome Presenting With Attacks of Abdominal Pain, Nausea, Vomiting, and Diarrhea

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ABSTRACT

The etiology for concurrent attacks of abdominal pain, nausea, vomiting, and diarrhea can be obscure. Mast cell activation syndrome is not usually considered in this differential diagnosis. A 53-year-old paint salesman suffered severe attacks of these symptoms for the 3 decades of his career. Nortriptyline, loperamide, hyoscyamine, and ondansetron failed to address his symptoms. Mast cell activation syndrome was ultimately diagnosed. Intravenous mast cell-targeted therapy reduced severity of attacks. Multiple oral mast cell-targeted treatments were ineffective, but addition of low-dose imatinib resulted in dramatic improvement. Recognition that paint-fume exposure-triggered attacks led to behavioral modifications which further reduced symptoms.

KEYWORDS: abdominal pain; diarrhea; imatinib; mast cell activation syndrome; nausea; vomiting

INTRODUCTION

Concurrent attacks of abdominal pain, nausea, vomiting, and diarrhea can be caused by Crohn's disease, dysmotility, small bowel obstruction, small intestinal bacterial overgrowth, celiac disease, alpha-gal syndrome, neuroendocrine tumors, cyclic vomiting syndrome, cannabinoid hyperemesis syndrome, porphyria, pancreatitis, heavy metal toxicity, hereditary angioedema, median arcuate ligament and other vascular compression syndromes, splanchnic artery aneurism, ischemic vascular disorders, familial Mediterranean fever, mastocytosis, and mast cell activation syndrome (MCAS).[1]

Mastocytosis is a rare mast cell activation disease which is usually a low-grade malignancy with an incidence 0.89 cases/100,000 persons-per-year.[2] By contrast, MCAS is a common mast cell activation disease with a prevalence estimated to be 17%-20% in Western populations.[3,4] MCAS is an under-recognized, chronic multisystem disorder caused by inappropriate, aberrant mast cell (MC) activation.[5]

Widespread systemic symptoms are frequently reported by patients with MCAS and are often mistaken by physicians as functional and sometimes fictitious or somatization disorders. This syndrome can be diagnosed by medical history and measurable biomarkers.[6] Beyond avoiding triggers, the best therapy is directed at modulating MC activation and the effects of MC mediators. Although many of these therapies are over-the-counter medications or simple prescriptions, a minority require aggressive therapy.[7]

We present a newly diagnosed patient with MCAS who suffered for 3 decades with attacks of abdominal pain, nausea, vomiting, and diarrhea often triggered by chemical exposure and in whom MC-targeting imatinib proved distinctly helpful.

CASE REPORT

A 53-year-old White man had consultation for attacks of diffuse, crampy abdominal pain; nausea; vomiting; and diarrhea starting at the age of 21 years. He went to emergency departments 6 times and urgent care centers 4 times. He was hospitalized 3 times. Attacks

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occurred every 2 weeks and lasted 1 to 3 hours. During severe attacks, he had 10 to 20 bouts of vomiting and 5 bouts of diarrhea, and these could last 2 to 3 days. Routine laboratory studies were normal. Abdominal computerized tomography examinations were normal during three attacks. None of the physicians who saw him over 32 years were able to provide a diagnosis or treatment plan. In the last 15 years, he also noticed daily postprandial bloating, unpleasant odor flatus, and bad breath. In the past, other gastroenterologists gave him a variety of treatments including nortriptyline, loperamide, hyoscyamine, and ondansetron, which failed to give relief.

Normal tests obtained by prior doctors included biopsies of the grossly normal stomach, duodenum, colon, and ileum using hematoxylin and eosin staining, capsule endoscopy, computed tomography angiography, blood count, complete metabolic profile, C-reactive protein, C1 esterase inhibitor, C4, urinary porphobilinogen, metanephrine metabolites, vasoactive intestinal peptide, and heavy metals.

Author L.B.W. started to see the patient 4 years before submission of this report. Abnormal tests obtained at that time included barium small bowel follow-through examination immediately after an attack demonstrating thickened folds in the small intestine and rapid transit to the colon (Figure 1). When relatively asymptomatic, his plasma prostaglandin D2 was 201 pg/mL (normal 35–115). The other 6 MC mediators obtained between attacks were normal, including repeating serum tryptase 6 hours after an attack started. Ideally, the repeat tryptase would be checked within 4 hours. Further history revealed that during attacks, his small cutaneous abdominal wall hemangiomas temporarily increased in size and number and were painful, and he suffered cognitive dysfunction and heartburn (all common in MCAS). The presence of MC symptoms in 2 or more systems (gastrointestinal, dermatologic, and neuropsychiatric), an abnormal MC mediator (prostaglandin D2), and the ultimate response to MC-directed therapy fulfilled the consensus-2 criteria for MCAS.[5] In light of the epigenetic factors which likely give rise to MCAS, the syndrome invariably starts with a variety of problems in childhood (such problems can include recurrent infections, gastrointestinal symptoms, atopic disorders, and headaches) and worsens over time (eg, fatigue, bruising, tinnitus, menorrhagia). In childhood, he had severe asthma and hives.

There was minimal benefit from standard oral MC therapy used over the course of 2 years: gluten and dairy-free diet, H1 and H2 receptor blockers twice daily, vitamins C and D, quercetin, low-dose naltrexone, aspirin, cromolyn, and lorazepam. Two courses of rifaximin 18 months apart for presumed small intestinal bacterial overgrowth reduced gas symptoms and seemed to temporarily reduce frequency of the attacks. He was not eligible for omalizumab since he did not have asthma, urticaria, anaphylaxis, or IgE-induced food allergies. A standardized regimen of intravenous diphenhydramine 50 mg, famotidine 20 mg, methylprednisolone 40 mg, and lorazepam

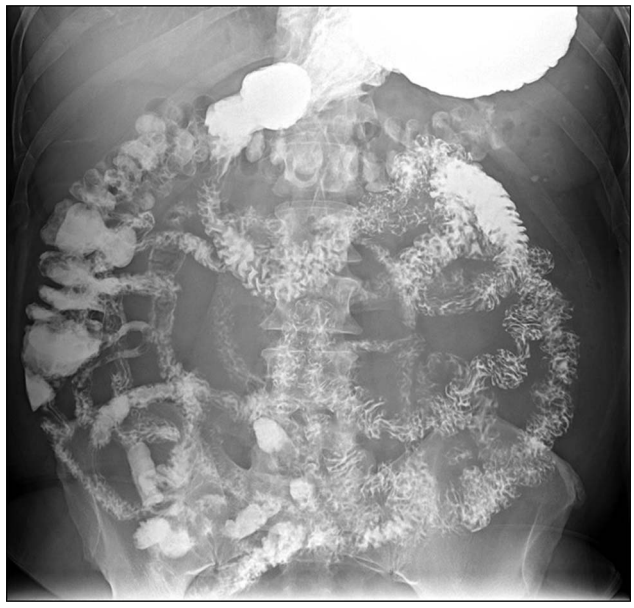

Figure 1. Barium small bowel follow-through imaging immediately after recovery from an attack managed in the hospital. There was diffuse fold thickening within the small bowel, mostly notably within the ileum, which demonstrates a jejunal fold pattern. There was rapid transit from the stomach to the colon.

1 mg reduced the severity of and/or aborted attacks in the emergency department, urgent care, and hospital.

After his last hospitalization in 2020, oral imatinib 200 mg daily was prescribed. Within 1 month, imatinib prevented severe attacks requiring hospitalization, emergency department, and urgent care. Mild attacks continued at home. Further history revealed that his worst attacks were precipitated by prolonged work-related exposure to paint fumes. Accordingly, he was told to stop this exposure. By doing so, the attacks stopped. He retired 1 year ago and has maintained a complete remission of abdominal pain, nausea, vomiting, heartburn, and cognitive dysfunction for 2 years. Owing to his present health status and the impact of MCAS on his life, he asked to extend the duration of low-dose imatinib. Safety laboratory results are monitored every 3 months.

DISCUSSION

MCAS is usually caused by somatic genetic mutations in MC regulatory genes causing dysregulated production and release of a large variety of potent mediators.[8,9] These mediators result in an often life-time multisystemic disease with inflammatory and allergic disorders.[5] Gastrointestinal symptoms are common in MCAS and cause poor quality of life.[10] In a cohort study of 175 newly diagnosed patients with MCAS presenting to a gastroenterologist with refractory gastrointestinal symptoms, abdominal pain was present in 86%, bloating in 68%, diarrhea in 65%, nausea in 63%, constipation in 63%, heartburn in 55%, and dysphagia in 33%.[11] By contrast, in a case series of 413 newly diagnosed patients with MCAS who presented to a hematologist with obscure multisystemic disorders experienced

nausea in 57%, heartburn in 50%, abdominal pain in 48%, alternating constipation and diarrhea in 36%, dysphagia in 35%, diarrhea in 27%, and constipation in 14%.[6]

Patients with MCAS often respond to elimination of gluten, dairy, and/or high histamine foods.[7] Many other triggers can play significant roles in MC activity (Table 1). MCAS-driven chemical intolerance (ie, toxicant-induced loss of tolerance) to volatile organic chemicals was seen in the patient presented in this study.[12] Antihistamines, flavonoids, vitamins, cromolyn, aspirin, and montelukast are often effective.[7] Low-dose naltrexone and hydroxyurea can be effective.[13,14] Omalizumab can control urticaria, asthma, anaphylaxis, and food allergies and may help gastrointestinal symptoms.[15]

Imatinib is a tyrosine kinase inhibitor, helpful in rare cases of KIT-D816V-negative mastocytosis and has been reported useful in three patients with MCAS.[16–18] A cohort of 23 drug-refractory patients with MCAS who then were treated with imatinib by author (L.B.W.) were identified by a medical record search. Blood counts and liver profiles were obtained weekly for 1 month and then monthly. Eleven patients had clinical improvement and have remained on maintenance therapy for up to 4 years thus far. Benefits included a variety of gastrointestinal symptoms in most, fatigue and cognitive dysfunction in most, bone pain in one, myalgia in one, flushing in one, migraines in one, and reduction in anaphylaxis attacks in one. One patient was dependent on jejunal tube feeding and was able to switch to an oral diet. Six patients did not improve and stopped treatment. Eight patients had adverse events, and 6 of these stopped therapy. These included fatigue in 3, hand edema in 1, nausea in 2, headaches in 1, alopecia in 1, myalgias in 1, and increased liver enzymes in 1. These may have been drug induced, but we cannot rule out the role of excipients.

It is important to consider MCAS in the differential diagnosis of gastrointestinal symptoms, to offer aggressive medical therapy for diagnosed MCAS (including intravenous therapy when needed), and to identify MC triggers.

Table 1. Known triggers for mast cell activation in some patients

Allergens: Alpha-gal syndrome, inhaled allergens, insect bites, wasp/bee venom
Dietary: Alcohol, dairy, gluten, high histamine foods, lectins, specific allergies (IgE, IgG, or other mechanisms), idiosyncratic food sensitivity, yeast
Environmental and physical: Barometric pressure changes, cold, electromagnetic hypersensitivity, exercise, heat, hypoxia, scents/odors, ultraviolet light (fluorescent and sun), vibration
Foreign material: Amalgam, implants (mesh, orthopedic metal, plastic), silicone, surgical staples, tattoos, transdermal products (eg, adhesive material)
Hormones: Estrogen, menstrual periods, pregnancy
Infections: Bacterial, fungal, mycobacterial, parasitic, tick-borne infections, viral (especially COVID and EBV)
Medications: allergies, excipients[a], idiosyncratic reactions, imaging contrast, specific medicines (ACE inhibitors, anti-seizure, beta-adrenoceptor antagonists, antibiotics especially fluoroquinolones and sulfa drugs, ester based local anesthetics, muscle relaxants, narcotics, vaccines
Microbiome changes: Dysbiosis, small intestinal bacterial and fungal overgrowth
Stress: Emotional, physical, prolonged fasting, psychological, sleep deprivation
Toxins: Chemicals (eg, paint and petroleum-based volatile organic compounds, herbicides (atrazine and glyphosate), heavy metal poisoning, mycotoxins from toxic mold, polyethylene, polyurethane, salicylates (in foods and household and personal hygiene products), smoke (wood, tobacco, petroleum, etc.)

COVID, coronavirus disease; EBV, Epstein-Barr virus; IgE, immunoglobulin E; IgG, immunoglobulin G.
[a] Excipients include food coloring, inert material, preservatives, and material of capsule.

DISCLOSURES

Author contributions: LB Weinstock initiated the project, provided the case, and contributed to the manuscript and critically reviewed and revised the manuscript. M. Tenkhoff contributed to the manuscript, performed the review and summary of the records, and critically reviewed and revised the manuscript. J. Gutovich reviewed the radiographs, wrote the figure legend, and critically reviewed the manuscript. LB Afrin critically reviewed the manuscript and assisted with its writing. LB Weinstock is the article guarantor.

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