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CASE REPORT

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Successful targeted treatment of mast cell activation syndrome with tofacitinib

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Abstract

Mast cell (MC) activation syndrome (MCAS) is a collection of illnesses of inappropriate MC activation with little to no neoplastic MC proliferation, distinguishing it from mastocytosis. MCAS presents as chronic, generally inflammatory multisystem polymorbidity likely driven in most by heterogeneous patterns of constitutively activating mutations in MC regulatory elements, posing challenges for identifying optimal mutation-targeted treatment in individual patients. Targeting commonly affected downstream effectors may yield clinical benefit independent of upstream mutational profile. For example, both activated KIT and numerous cytokine receptors activate the Janus kinases (JAKs). Thus, JAK-inhibiting therapies may be useful against the downstream inflammatory effects of MCAS. The oral JAK1/JAK3 inhibitor, tofacitinib, is currently approved for rheumatoid arthritis and is in clinical trials for other chronic inflammatory disorders. Herein, we report two patients with MCAS who rapidly gained substantial symptomatic response to tofacitinib. Their improvement suggests need for further evaluation of this class of drugs in MCAS treatment.

KEYWORDS

mast cells, mast cell activation syndrome, KIT activation, JAK inhibitors, tofacitinib, rheumatoid arthritis, fibromyalgia, dysautonomia

1 | INTRODUCTION

Recently, a new understanding of mast cell (MC) disease has emerged, with allergy/atopy and rare, neoplastic mastocytosis comprising the readily recognizable tip of an iceberg of "MC activation disease" (MCAD), while the hidden bulk is complex, heterogeneous presentations of "MC activation syndrome" (MCAS) featuring chronic multisystem inflammation and sometimes also allergy/atopy and/or aberrant growth/development in various tissues.[1] Suggestions are emerging that MCAS often shares with mastocytosis the feature of heterogeneous mutational profiles (mostly somatic) in MC regulatory genes, epigenes, and microRNAs driving intracellular perturbances leading to the disease's clinical phenomena. Targeting mutated proximal drivers (eg, constitutively activated KIT) is one therapeutic strategy, but mutational heterogeneity found to date suggests targeting downstream effectors upon which proximal drivers converge may be more efficient. For example, inhibition of pro-inflammatory Janus kinases (JAK1, JAK3), whether activated by KIT or by certain ligands (eg, certain interferons and interleukins) binding with their receptors, might help control MCAD symptoms. Oral JAK1/JAK3 inhibitors (eg, tofacitinib) have been developed for chronic inflammatory disorders including methotrexate-intolerant or methotrexate-unresponsive rheumatoid arthritis (RA) and inflammatory bowel disease and appear safe and effective. Independent of upstream issue(s), tofacitinib might downregulate some JAK-mediated effector T-cell responses seen in MCAD. We report two patients with the MCAS form of MCAD who enjoyed rapid, substantial improvement with tofacitinib.

2 | CASE 1

A 55-year-old businesswoman sought evaluation in July 2014 (the same month she was diagnosed with seronegative, erosive RA and

TABLE 1 Symptoms and key laboratory results at initial evaluation for MCAS

	Symptoms	Key laboratory results (normal range [references in Data S1])
Case 1	Feeling cold much of the time (especially when her symptoms flared), occasional headache, episodic cognitive dysfunction, constant bilateral tinnitus, diffusely migratory pruritus, irritated eyes, nasal irritation and copious coryza, irritated throat during flares, dyspnea (often driving emergent evaluation), occasional proximal dysphagia, chest discomfort/heaviness, palpitations (including occasional spontaneous waking with such; resolved with antihistamines), nausea, diarrhea, diffusely migratory abdominal pain, marked abdominal bloating and diffuse edema with weight gain for several days upon eating certain foods, diffusely migratory edema, diffusely migratory paresthesias, waxing/waning bilateral cervical adenitis (but not adenopathy), frequent presyncope (resolved with antihistamines), occasional aquagenic syncope, progressive deterioration of dentition despite good hygiene, alopecia, longitudinal ridging, and loss of growth plates in all nails	Serum tryptase: 4 ng/mL (<11) Plasma histamine: 9 nmol/L (0-8) 24-h urinary prostaglandin D_2: 437 ng/24 h (100-280) KIT-D816V mutation analysis (peripheral blood): negative
Case 2	Subjective (but usually not objective) fevers, flushing, feeling cold much of the time, fatigue (often to the point of exhaustion), malaise, headaches, diffusely migratory aching/pain, diffusely migratory pruritus, unprovoked soaking sweats, unprovoked fluctuations in weight and appetite, irritation of the eyes, acute brief inability to focus vision, easy bruising, sinonasal congestion, coryza, postnasal drip, nasal sores, irritation of the throat, dyspnea, proximal dysphagia, palpitations, non-anginal chest discomfort/pain, gastroesophageal reflux, nausea, vomiting, diarrhea alternating with constipation (improved with various mast cell stabilizers), "constant" diffusely migratory abdominal discomfort including (usually postprandial) bloating (modestly improved with dietary restrictions), urinary frequency and hesitancy and urgency, diffusely migratory weakness, diffusely migratory edema, diffusely migratory tingling/numbness (typically about the distal extremities), diffusely migratory adenopathy and adenitis about the bilateral cervical regions, orthostatic and non-orthostatic presyncope, syncope, cognitive dysfunction (particularly memory, concentration, and word finding), premature hair greying, hair loss, deterioration of dentition despite good attention to dental hygiene, brittle nails, diffusely migratory rashes (typically patchy macular erythema), and poor healing in general	Plasma heparin: 0.07 anti-Factor Xa units/mL (≤0.02) Serum chromogranin A: 160 ng/mL (0-95) Gastric biopsy: 27 mast cells per high power field by bright CD117 staining (≤20) Colonic biopsy: 27 mast cells per high power field by bright CD117 staining

started on leflunomide) for the MCAS she suspected underpinned her chronic multisystem polymorbidity of inflammatory theme. As typical in MCAS,[1] her full history is complex and is provided in the Data S1. In summary, since puberty, she had suffered chronic inflammatory issues in the gastrointestinal, genitourinary, lymph node, respiratory, cardiovascular, musculoskeletal, and central and peripheral nervous systems. Allergic and tissue growth/development issues were present, too. Symptoms reported, and key laboratory results found, at initial evaluation for MCAS are shown in Table 1.

She was diagnosed with MCAS.[1] She was taking cetirizine, famotidine, cromolyn, ketotifen, diphenhydramine, montelukast, and thyroid replacement but was still significantly symptomatic. Before other medication trials could be pursued, her rheumatologist started her in October 2014 on tofacitinib 5 mg twice daily for leflunomide-refractory RA. Multiple symptoms immediately improved. By Week 2, all symptoms had virtually completely remitted, including postprandial abdominal distention. Other medications were successfully reduced. Occasional extra doses for symptomatic flares (roughly twice yearly) reliably, quickly stabilized her. In May 2016, she switched to extended-release tofacitinib 11 mg once daily, immediately reporting further "improved stability" and additional reduction in food sensitivities. The only toxicity seen was mild abdominal pruritus with extended-release product, suggesting reaction to an excipient in extended-release, but not immediate-release, product. Her remission has continued uninterrupted for 30 months to date.

3 | CASE 2

The 29-year-old daughter of Case 1 sought evaluation in June 2015 for the MCAS she, too, had come to suspect underpinned her own chronic multisystem polymorbidity of inflammatory theme (full history in the Data S1). Since birth, she had steadily suffered inflammation in the same range of systems as her mother, plus dermatologic issues. Symptoms at the initial evaluation for MCAD, and key laboratory test findings, are shown in Table 1. She was diagnosed with MCAS. Hydroxyzine 10 mg as needed proved modestly helpful, but before trying other MCAS-directed therapy, in June 2016 she was able to begin immediate-release tofacitinib 5 mg twice daily. She, too, enjoyed rapid, substantial improvement including increased energy and alertness, better sleep, reduced acne/folliculitis, and decreased diarrhea. Oral cromolyn was successfully reduced. Other symptoms continued without improvement. In early January 2017, she began extended-release tofacitinib 11 mg once daily. She saw immediate further improvement with increased energy and reduced arthralgias. Daily nausea and diarrhea resolved.

Frequent headaches resolved. Folliculitis reduced further. Her improvements have continued for 10 months to date. No new symptoms of disease or treatment have emerged.

4 | DISCUSSION

These cases are the first reports of safe, effective use of tofacitinib in recognized MCAS. Multiple traditional interventions had yielded weak responses. JAK1/JAK3 inhibition with immediate-release tofacitinib then provided prompt, significant improvement; extended-release product provided even more improvement.

Tofacitinib treatment is associated with reversible reduction in natural killer cells. Across seven placebo-controlled clinical trials of tofacitinib in RA leading to registration, serious infections and a variety of malignancies were observed; although the number of subjects affected was very small, the product has a black-box warning to this effect. Viral reactivation was occasionally observed. The only other adverse reactions observed in at least 1% more subjects treated with 5 mg twice daily than in placebo-treated subjects were diarrhea, nasopharyngitis, upper respiratory tract infection, and headache (all ~4% vs placebo ~2%-3%). Significant decreases in lymphocytes or neutrophils, or increases in hepatic transaminases, occurred in ~1% of tofacitinib-treated subjects.[2]

Our observations are clinical. Furthermore, our patients are related and thus might have unique genetic susceptibility which might make tofacitinib more likely to be uniquely beneficial in them and less generalizable to the MCAS population at large. Much investigation remains to be done, including determination of MC mutational profiles (presumably sharing at least some mutations in common even though MCAS family studies suggest different affected family members typically bear different (somatic) mutations in MC KIT[3]), but we feel the new direction suggested by these cases is important and bears timely reporting.

With emergence of symptoms earlier, and more severely, in the daughter compared to her mother, these cases demonstrate multigenerational "anticipation" expected in epigenetically rooted diseases as suspected of MCAS.[3]

Our patients' improved response with extended-release tofacitinib suggests revival of JAK1/JAK3 activity after clearance of immediate-release drug (terminal phase half-life 3.2 hours[4]) is sufficient to sustain clinically significant activation.

The responsiveness of the mother's postprandial abdominal bloating to tofacitinib is noteworthy. Bloating is common in MCAS[1] and frustrates patients and providers. Such patients often complain their abdomens painfully transform from baseline/scaphoid to "nine months pregnant" within minutes. Obstruction or bowel angioedema is often suspected but rarely found, even upon acute evaluation. An alternative explanation might be acute bowel dysautonomia, similar to other dysautonomias (eg, postural orthostatic tachycardia syndrome, pseudo-seizures) seen in MCAS. Given (i) relative MC abundance in the GI tract, (ii) abutment of neurons and MCs and their constant mediator "cross-talk",[5] and (iii) the fact that such distention commonly is postprandial and whole-gut (rather than only near just-ingested food), one model for such episodes is dietary antigens provocative to dysfunctional MCs may be triggering proximal GI tract MCs which interact with abutting neurons to spark diffuse visceral dysautonomia manifesting as abrupt abdominal distention. The possibility that JAK activation may be relevant in some dysautonomias, and therefore that JAK inhibitors may be useful in such conditions, should be considered.

In conclusion, tofacitinib appears to downregulate inflammatory phenomena associated with MCAS in our patients and thus may help other patients with MCAS, but its risks and expense suggest its optimal role may be as later-line therapy. Much research remains to clarify the roles of JAK inhibitors in management of MCAS, but formal clinical trials of tofacitinib in MCAS seem warranted.

AUTHORS' INFORMATION

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COMPETING INTERESTS

None. Dr. Afrin was a consulting diagnostician in the patients' care; he conceived of and wrote the original draft of the manuscript, participated in editing, and submitted the manuscript and has no conflicts relevant to this project. Dr. Glover was involved in the patients' care, participated in the editing of the manuscript, and has no conflicts relevant to this project. She has received research funding from Takeda, Abbvie, UCB, BMS, Celgene, Janssen, and Pfizer. She has previously served on speakers bureaus for Takeda, Janssen, and Abbvie. Drs. Zito, Fox, and Choe were involved in the patients' care, participated in the editing of the manuscript, and have no conflicts relevant to this project.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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