Mast Cell Activation Syndrome Masquerading as Agranulocytosis

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ABSTRACT Acquired agranulocytosis is a rare, life-threatening disorder. The few known causes/associations usually are readily identifiable (e.g., drug reaction, Felty syndrome, megaloblastosis, large granular lymphocytic leukemia, etc.). We report a novel association with mast cell disease. A 61-year-old morbidly obese man developed rheumatoid arthritis unresponsive to several medications. Agranulocytosis developed shortly after sulfasalazine was started but did not improve when the drug was soon stopped. Other symptoms across many systems developed including hives and presyncope. Marrow aspiration and biopsy showed only neutropenia. Serum tryptase was mildly elevated; urinary prostaglandin D_2 was markedly elevated. Other causes were not found. Mast cell activation syndrome (MCAS) was diagnosed. Oral antihistamines, montelukast, and cromolyn were unhelpful; aspirin was initially felt contraindicated. Imatinib immediately increased neutrophils from 0% to 25% but did not help symptoms; subsequent addition of aspirin increased neutrophils further and abated symptoms. Different presentations of different MCAS patients reflect elaboration of different mediators likely consequent to different *Kit* mutations. Mast cells (MCs) help regulate adipocytes, and adipocytes can inhibit granulopoiesis; thus, a *Kit*-mutated MC clone may have directly and/or indirectly driven agranulocytosis. MCAS should be considered in otherwise idiopathic agranulocytosis presenting with comorbidities best explained by MC mediator release.

INTRODUCTION

Acquired agranulocytosis is a rare (annual incidence 1–5 cases per million population[1]), acute, life-threatening illness characterized by severe deficit in circulating granulocytes (principally neutrophils) in the absence of known causative diseases (e.g., megaloblastic or aplastic anemia, Felty syndrome, large granular lymphocytic leukemia, liver disease) or exposure to cytotoxic chemotherapy. Most incidents of agranulocytosis appear to be complications of drug therapies of various sorts (e.g., antithyroid drugs, sulfasalazine, clozapine) and resolve soon after discontinuation of the offending agent. Mast cell disease (MCD) has not previously been implicated in agranulocytosis. Reported here is the first case of agranulocytosis for which mast cell activation syndrome (MCAS) appeared to be the underlying cause and which responded to treatment for MCAS.

CASE REPORT

In May 2007, a 61-year-old morbidly obese hypertensive diabetic black male veteran, diagnosed by a rheumatologist 4 years earlier with rheumatoid arthritis (RA), was referred for evaluation of agranulocytosis. Comorbidities included depression, anxiety, fatigue, chronic atrial fibrillation, impotence, gynecomastia, mild dyspnea, gastroesophageal reflux disease, obstructive sleep apnea, and poor tolerance of annual influenza vaccinations; he smoked one pack of cigarettes daily. Although his rheumatoid factor alternated between negative and low titers, his anti-cyclic citrullinated peptide antibodies were persistently and strongly positive (144–148 units, normal less than 20 units). Viral hepatitis B and C testing was negative. There were no classic symptoms or signs of pulmonary or miliary tuberculosis, and purified protein derivative skin testing was negative with positive controls. His fluctuating/intermittent symptoms of RA (chiefly stiffness, pain, and swelling of multiple proximal interphalangeal joints and wrists, worse in the morning) did not clearly respond to sequential trials of acetaminophen, ibuprofen, naproxen, diclofenac, methotrexate, and hydroxychloroquine, and though symptoms responded variably to repeated trials of prednisone, they invariably soon relapsed with steroid tapering or discontinuation. His RA symptoms, although persistent, were not felt by his rheumatologists to be sufficiently severe to warrant a trial of a tumor necrosis factor antagonist. Sulfasalazine was next added by his rheumatologist to hydroxychloroquine. Prior complete blood counts and differentials had been normal for at least a decade; in particular, the patient had maintained normal blood counts during methotrexate treatment and for 13 months afterward until sulfasalazine was begun. Immediately after beginning sulfasalazine in 2004, the patient was lost to follow-up to his rheumatologist for the next 2 years, but another provider discontinued the drug (2 months after it had been started) for inefficacy without noting that agranulocytosis (leukocytes approximately 3,000/mm^3, neutrophils generally 0.5%–3%, absolute neutrophil counts typically 0–200/mm^3) and monocytosis (persistently about 30%) had developed within 4 weeks of starting the drug. No other medication changes correlated with this marked hematologic change. The hematologic abnormalities did not resolve following discontinuation of the drug. No other hematologic parameters were affected initially; splenomegaly was not apparent, and despite the fact that the agranulocytosis was not recognized until 36 months after sulfasalazine was stopped, no infectious

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complications developed except occasional upper respiratory syndromes in which no specific infectant was ever identified.

Once agranulocytosis was recognized, hydroxychloroquine was stopped, but agranulocytosis continued unchanged. Mild normocytic anemia (hemoglobin typically 11 g/dL, normal red cell distribution width) and mild thrombocytopenia (platelets typically 120,000/mm^3) emerged. Splenomegaly was not appreciated clinically or radiographically on computed tomography of the abdomen. Corrected reticulocyte count was normal. Serum cobalamin, folate, and ferritin levels were repeatedly normal, and serum iron levels were repeatedly low, consistent with anemia of inflammation. Total protein was consistently normal; albumin was consistently slightly low; and serum protein electrophoresis was not felt warranted. He was not felt by his rheumatologists to have any evidence of lupus or Sjögren's syndrome. Antinuclear antibody fluctuated between negative and titers up to 1:640 (homogeneous pattern) without any clear trend since initial detection 3 years before onset of agranulocytosis. Anti-double stranded DNA antibodies, anti-Smith antibodies, antiribonucleoprotein antibodies, and Sjögren's Syndrome A (SSA, Ro) and Sjögren's Syndrome B (SSB, La) antibodies, repeatedly checked after recognition of agranulocytosis, were consistently negative. Serum complement C3 and C4 levels were consistently normal. Erythrocyte sedimentation rates fluctuated between 10 and 111 mm/h but typically were about 40 mm/h. Multiple urinalyses from 1995 to 2011 were unremarkable. Marrow aspirate could not be obtained; marrow biopsy was normal except for left myeloid shift and neutropenia. Karyotype was normal. Chart review showed that in addition to his migratory arthritic symptoms, he had been complaining for many years of additional fluctuating/intermittent problems including headache, conjunctivitis, xerostomia, halitosis, oral mucositis, dry cough, night sweats, rash (never biopsied), and occasional presyncope; also noted were intermittent mild renal insufficiency and a persistent decrease in eosinophils from 1%–3% to 0%–0.3% which developed shortly before agranulocytosis was first recognized (and coincident with an episode of idiopathic worsening edema). Multiple ophthalmologic consultations from 2005 to 2011 were consistently unremarkable. Two weeks after the marrow biopsy, he developed a 24-hour period of hives all about his trunk (not biopsied), followed by appearance of a *Pseudomonas aeruginosa* sacral abscess which required surgical and medical management for 8 months before healing. Koebner phenomenon was not noted. Antineutrophil antibodies and antineutrophil cytoplasmic antibodies (p-ANCA and c-ANCA) were negative. Peripheral blood T-cell receptor gene rearrangement (TCRGR) study showed an unquantified clonal gamma chain rearrangement, but review of the peripheral smear and flow cytometry did not otherwise support a diagnosis of large granular lymphocytic leukemia, and no other evidence of a lymphoproliferative process could be found. He did not respond to extended trials of pegfilgrastim or abatacept (felt by the rheumatologist to be a safer option in this patient than a tumor necrosis factor antagonist).

In February 2009, underlying MCD was suspected as a potential cause of his particular assortment of chronic multisystem polymorbidity. Re-review of the marrow did not show increased mast cells (MCs). *Kit* gene sequencing was unavailable. Serum tryptase was only mildly elevated (15 ng/mL, normal 2–10 ng/mL). A 24-hour urinary prostaglandin D_2 (PGD_2) was markedly elevated (1,078 ng/24 h, normal 100–280 ng/24 h). Plasma histamine and 24-hour urinary *N*-methylhistamine levels were normal. The patient was not felt to be a candidate for additional biopsies. Given that the full range of findings in the case was consistent with MCD but that diagnostic criteria for systemic mastocytosis (SM) were not met and no other primary or secondary causes of MC activation were apparent, MCAS was diagnosed per proposed criteria available at that point and MCAS-directed therapy was felt warranted. Aspirin was initially avoided because of the frequent intolerance of aspirin in MCD and because of his chronic anticoagulation for atrial fibrillation. Trials of combined histamine (H_1 and H_2) blockade (loratadine and ranitidine), a leukotriene antagonist (montelukast), and oral cromolyn each proved unhelpful and were stopped.

Oral imatinib (100 mg/d) was begun in January 2010. The total leukocyte count and anemia did not initially improve, but platelets normalized within 2 months and, within just 1 month, neutrophils acutely improved to 25% of 3,200/mm^3 (from their 6-year record of nearly 0%) and eosinophils acutely improved to 0.5% (from their 6-year record of 0%). Monocytes decreased to 20%. No other clinical improvements were seen; indeed, chronic diarrhea, an episode of shingles in a left T8 distribution, and bilateral lower extremity cellulitis soon developed. Diarrhea was unresponsive to assorted antibiotics and was negative for *Clostridium difficile* toxin. Shingles were treated with valacyclovir. Cellulitis was treated with hospitalization and intravenous antibiotics which did not clearly help. Antihistamines were restarted and imatinib was increased to 200 mg/d and continued to be tolerated well, but these maneuvers did not help his symptoms and there was no further improvement in the granulocyte count. Enteric-coated aspirin was begun in June 2010 at 325 mg twice daily and was tolerated well. All nonarthritic symptoms (including diarrhea and cellulitis) improved significantly within 1 month; hematologically, neutrophils improved further to 41% (absolute neutrophil count 1,800/mm^3) and eosinophils improved to 3.1%. Leukopenia resolved as of February 2011; anemia resolved as of May 2011. Arthritic symptoms have improved modestly, and weight has not changed significantly. There have been no further episodes of presyncope, hives or other rash, or edema since aspirin was begun. As of July 2011, therapy has continued without change, there have been no therapeutic complications, and all clinical and laboratory improvements have been fully sustained.

DISCUSSION

Agranulocytosis usually is due to immune-mediated destruction of granulocytes and precursors idiosyncratically triggered by drug exposure and usually resolves quickly upon removal of the offending agent.[1] However, although agranulocytosis developed in this patient shortly after exposure to an agent (sulfasalazine) with a known risk for agranulocytosis, the condition oddly did not resolve upon removal of the offending agent. Autoimmunity likely was not the explanation for the agranulocytosis given: (1) the absence of detectable antineutrophil and other autoantibodies (except for inconsistent antinuclear antibody titers long predating onset of agranulocytosis), (2) the rapid response to imatinib (which is not known to block autoantibodies or directly inhibit autoantibody production), and (3) well-established general antibody kinetics. Clinical and radiographic absence of splenomegaly, along with lack of response to abatacept, reasonably excluded Felty syndrome. There was no clear evidence of lymphocytic disease in this patient; gamma-TCRGR studies often are positive either falsely or without any identifiable lymphocytic disease. Furthermore, the collection of symptoms accompanying this patient's agranulocytosis was more consistent with MCD. Although World Health Organization criteria for SM[2] were not met, MCAS remained possible and was initially supported by the history and the marked PGD_2 elevation, which is highly sensitive and specific for MC activation.[3] Of note, emergence of new clinical phenomena in the individual MCD patient (such as agranulocytosis in our patient) may be triggered by patient stress or exposure to new antigens such as infectants or drugs that provoke unstable MCs to generate new patterns of aberrant mediator expression.

Slightly varying systems of diagnostic criteria for MCAS have recently been proposed by several groups,[4–6] and include a history consistent with episodic aberrant MC mediator release, presence of elevated MC markers in the blood or urine, response to empiric MC-directed therapy, and absence of other known primary or secondary causes of MC activation such as SM, allergy, and physical urticaria. Although global consensus regarding diagnostic criteria for MCAS has not been reached, recognition by many groups of MCAS as a subset of MCD which is distinct from the SM subset offers the opportunity for diagnostic labeling (and therapeutic intervention) of patients who clinically appear to have SM but who do not meet all the World Health Organization criteria for SM.

MCs elaborate more than 200 mediators affecting functions throughout the body.[7] MCs are thought to mostly originate in the bone marrow but quickly disperse via the circulation. MCs are present sparsely in every tissue in the human body but tend to reside at environmental interfaces and near lymphatic and blood vessels, abetting the MC sentinel function. MCs in different tissues harbor different mediators as needed for local homeostasis. Different symptom complexes and laboratory findings in different MCAS patients (Tables I and II) likely result from different aberrant mediator expression patterns driven by the many different mutations which have been found (in *Kit* and other MC regulatory proteins) in these patients.[8] For example, because of the variability of their specific patterns of aberrant mediator expression, patients with MCD have highly variable hematologic presentations[9] including normal, excess, or low erythrocytes, leukocytes, and/or platelets, but in the absence of associated clonal hematologic neoplasms, extreme cytopenias appear uncommon. However, as shown in this case, agranulocytosis appears to be one

TABLE I. Symptoms Seen in Mast Cell Disease

System	Potential Symptoms of Mast Cell Disease
Constitutional	Fever and/or chills (or a sense of feeling cold much of the time), fatigue/malaise, sweats/flushing, pruritus, increased or decreased appetite/weight, environmental sensitivities (often odd)
Ophthalmologic	Irritated eyes, lacrimation, conjunctivitis, difficulty focusing, lid tremor/tic
Otologic	Hearing deficit, tinnitus
Oral/Oropharyngeal	Pain or burning, leukoplakia, throat discomfort
Lymphatic	Adenopathy, usually modest in size, often tender, sometimes focal, sometimes migratory
Pulmonary	Rhinosinusitis, laryngitis, cough (usually dry), dyspnea (often subtle)
Cardiovascular	Presyncope and/or syncope, labile blood pressure, palpitations, chest pain, vascular disease, migratory edema
Gastrointestinal	Nausea, vomiting, diarrhea and/or constipation, abdominal pain, malabsorption
Genitourinary	Chronic kidney disease interstitial cystitis (including frequent culture-negative urinary tract "infections"), chronic pelvic/low back pain
Musculoskeletal	Migratory muscle, joint, and/or bone discomfort
Neurologic	Headache, peripheral sensory and/or motor neuropathy
Psychiatric	Mood disturbances, anxiety disorders, psychoses, cognitive dysfunction, insomnia
Dermatologic	Often migratory rashes and lesions of many sorts, dermatographism
Hematologic	Arterial and/or venous thromboembolic disease, bruising/bleeding
Endocrinologic/Metabolic	Dysmenorrhea, osteosclerosis or osteoporosis, thyroid disease, dyslipidemia, hyperferritinemia, possibly diabetes mellitus
Immunologic	Hypersensitivity reactions, increased risk for malignancy and autoimmunity, increased susceptibility to infection, impaired healing

Most are low grade and episodic or fluctuant but sometimes can be severe and/or persistent.

TABLE II. Laboratory Anomalies Commonly Seen in Mast Cell Disease

Tissue/System	Potential Laboratory Manifestations of Mast Cell Disease
Mast Cells	Elevations in serum tryptase (strongly in SM, though little to none in MCAS), plasma or urinary PGD_2 or metabolites, plasma or urinary histamine or metabolites, plasma heparin, serum chromogranin A
Lymphatic	Pathology of enlarged nodes usually shows a reactive lymphocytosis or sometimes an atypical nonspecific lymphoproliferative disorder
Hematologic	Increases or decreases in red cells (and hemoglobin and hematocrit), white cells, and/or platelets; chronic mild monocytosis or eosinophilia or basophilia; increases or decreases in prothrombin time and/or partial thromboplastin time; in contrast to SM, in MCAS the marrow usually does not show increased, or even flow cytometrically aberrant, MCs and marrow histology is often interpreted as normal or as non-specific myelodysplasia/myeloproliferation; standard cytogenetic studies are almost always normal or yield culture failure
Endocrinologic/Metabolic	Abnormal electrolytes, mildly elevated transaminases and alkaline phosphatase, elevated ferritin (sometimes markedly so)

Most are low grade and episodic or fluctuant but sometimes can be severe and/or persistent. With the exception of tryptase, PGD_2, histamine, and heparin, the findings above are not thought to be highly specific to MCD but are not uncommonly seen in MCD.

possible hematologic presentation, and MCAS has been reported recently to cause another isolated severe hematologic abnormality, too (pure red cell aplasia).[10] Associations between MCD and inflammatory/autoimmune disorders such as RA are being increasingly recognized.[11,12] Recognition of MCAS often depends on reconsideration of unifying diagnoses which can biologically reconcile multiple problems poorly responsive to specific therapies. MCAS is thought to be considerably more prevalent than the rare SM, which increasingly is appearing to be driven by the rare *KIT*-D816V mutation.[8]

Kit stem cell factor receptor and tyrosine kinase is expressed at high levels on the MC surface and is critical for many MC functions including activation.[13] Furthermore, the stroma vascular fraction of white adipose tissue is a reservoir of functional MC progenitors,[14] and marrow adipocytes can block granulopoiesis through neuropilin-1-mediated inhibition of granulocyte colony stimulating factor.[15] Although not proven to be the cause of agranulocytosis in this morbidly obese patient, this constellation of recent research findings suggests (1) MCs may be involved in regulating adipocyte function and (2) a *Kit*-mutated MC clone may have driven adipocyte production of granulopoiesis-inhibiting factors in this case. Alternatively, mediators released by the posited MC clone could have directly inhibited granulopoiesis. Most likely, the full spectrum of problems seen in this patient were the result of both direct and indirect effects of released MC mediators; for example, the monocytosis could have been driven by release of monocyte/macrophage colony stimulating factor both directly from the MCs[7] and indirectly from the MC mediator-driven adipocytes.[15]

Despite their histories of chronic multisystem polymorbidity often spanning decades, most patients with MCAS can gain significant improvement with MC-directed therapies which include inhibitors of mediator production (e.g., aspirin), antagonists of released mediators (e.g., antihistamines), and MC stabilizers (e.g., cromolyn, imatinib). As illustrated by the present case, there are no methods presently available to predict which therapies will best manage which patients (i.e., a given symptom in different patients does not necessarily respond to the same therapy in each patient), so persistence is required in stepping through available treatments. The great longevity of MCs, together with their relative resistance to cytotoxic chemotherapy, suggests that effective therapy may need to be continued indefinitely.

Imatinib is a potent inhibitor of both wild-type *Kit* and certain mutations (though typically not the D816V mutation of SM) and has shown clinical activity at daily doses as low as 100 mg.[16] There are case reports of response of RA to imatinib (e.g.,[12]), but absent evidence of SM or other *Kit*-modulated disease, prompt improvement only in this patient's agranulocytosis and thrombocytopenia (i.e., not also his RA symptoms) upon exposure to imatinib suggests that MCAS was more likely than RA to be the cause of his agranulocytosis and thrombocytopenia, and the ensuing symptomatic improvement with aspirin (commonly employed to help control systemic MCD[3]) further supports a diagnosis of MCAS as the etiology of most or all of this patient's problems. (The patient's prior lack of response in his RA to nonsteroidal anti-inflammatories discounts the likelihood that his improvements with aspirin arose more from its targeting of RA than MCAS.) Given the additional improvement in neutrophil count with the addition of aspirin, it is unclear whether aspirin alone (i.e., without imatinib) could have achieved the final neutrophil count seen with imatinib plus aspirin, and a trial of aspirin alone may be warranted in this case given the expense of imatinib. However, it is clear imatinib alone safely and effectively addressed the patient's agranulocytosis, and the costs of the patient's care before effective control of his MCAS likely exceeded the cost of imatinib.

CONCLUSIONS

MCAS should be considered in persistent agranulocytosis presenting without a classic pattern of drug association or detectable antigranulocyte autoimmunity and with other comorbidities best explained by MC mediator release. MCAS may also be a consideration in other cases

of treatment-refractory chronic multisystem polymorbidity, particularly in patients harboring idiopathic inflammatory illnesses. Patients with MCAS often improve with persistent trials of assorted MC-directed therapies.

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