



CASE REPORT

Successful treatment of mast cell activation syndrome with sunitinibLawrence B. Afrin¹, Frank M. Cichocki¹, Kamal Patel², Gerhard J. Molderings³¹Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN; ²CARTI Hematology/Oncology, Little Rock, AR, USA; ³Institute for Human Genetics, University of Bonn, Bonn, Germany**Abstract**

Mast cell (MC) activation syndrome (MCAS) is a recently recognized, likely prevalent collection of heterogeneous illnesses of inappropriate MC activation with little to no MC neoplasia likely driven by heterogeneous patterns of constitutively activating mutations in MC regulatory elements including various tyrosine kinases (TKs, dominantly KIT). MCAS typically presents as chronic multisystem polymorbidity of generally inflammatory \pm allergic theme. As with indolent systemic mastocytosis (SM), treatment of MCAS focuses more against MC mediators than MC neoplasia, but some cases prove refractory even to the TK inhibitor (TKI) imatinib reported useful both in uncommon SM cases not bearing SM's usual imatinib-resistant KIT-D816V mutation and in some cases of MCAS (which rarely bears KIT-D816V). Most allergy is principally a MC activation phenomenon and sunitinib is a multitargeted TKI shown helpful in controlling a murine model of oral allergy syndrome. We present the first report of use of sunitinib in life-threatening MCAS refractory to multiple agents including imatinib achieving immediate, complete, sustained, non-toxic remission suggesting a new option for treatment of aggressive MC disease.

Key words mast cell; mast cell activation disease; mast cell activation syndrome; tyrosine kinase inhibitor; sunitinib

Correspondence Lawrence B. Afrin, MD, Division of Hematology, Oncology, and Transplantation, University of Minnesota, 420 Delaware St. SE, MMC 480, Minneapolis, MN 55455, USA. Tel: +1 612 624 0123; Fax: +1 612 625 6919; e-mail: afrinl@umn.edu

Accepted for publication 10 June 2015

doi:10.1111/ejh.12606

Long thought little more than rare mastocytosis and allergic phenomena, the scope of mast cell (MC) disease recently has widened to recognize MC activation syndrome (MCAS), featuring inappropriate MC mediator release (i.e. MC activation) now seen universal in MC disease but with little of the MC neoplasia hallmarking mastocytosis (1). Via many MC mediators, MCAS presents heterogeneously as chronic multi-system polymorbidity, punctuated by flares, of generally inflammatory \pm allergic theme. Understanding of genetic roots of MC activation disease [MCAD, the new overarching term for all MC disease (1)] began emerging in 1993 upon finding the recurrent, oncogenic D816V activating mutation of the MC's principal regulatory element, transmembrane receptor tyrosine kinase (TK) KIT, in systemic mastocytosis (SM) (2). More recently, menageries of KIT mutations (seemingly non-recurrent and not affecting codon 816) were found in MCAS (2), suggesting 'secondary' or 'idiopathic' cases might be 'primary' upon closer examination.

Advancing investigations now suggest most MCAD harbors multiple, usually somatic mutations across many MC regulatory genes, epigenes, and microRNAs (2).

MCAD's behavior in the individual likely results from specific mutations driving specific patterns of constitutive MC activation and aberrant reactivity. Treatment may eventually be genotypically defined, but MC mutation testing remains limited in most clinical laboratories (essentially just KIT-D816V), forcing empiric selection of inhibitors of MC mediator production/action. Inexpensive interventions (e.g. histamine H₁ and H₂ receptor antagonists (H1RA, H2RA)) are commonly tried first, but many remain symptomatic, some severely so. KIT-targeting TK inhibitors (TKIs) have been tried, typically with imatinib [found useful in some cases of MCAS and in some uncommon SM cases which, like most MCAS cases, do not bear KIT codon 816 mutations (2)]. Sunitinib is a multitargeted TKI used in gastrointestinal stromal tumor (GIST, also largely driven by

KIT mutations) and other applications, but not yet MCAD. We now report successful use of sunitinib in life-threatening, imatinib-resistant MCAS.

Case report

A healthy 28-year-old woman (allergic only to erythromycin) entered military service in February 2010. In March 2011, preparing for deployment, she was vaccinated against smallpox, anthrax, and typhoid. She quickly developed fever, fatigue, and nausea, which soon partially improved. Heartburn, regular postprandial abdominal pain, dizziness, and dyspnea then emerged. En route to Afghanistan a month later, fever relapsed, and diffuse aching emerged. Clinical evaluation was non-diagnostic. Fatigue was severe; she slept through sirens. She began avoiding meals but lost weight and was ordered to eat, causing headache, panic, flushing, blood pressure lability, disorientation, and syncope.

Heat exhaustion treatment proved unhelpful. Anaphylaxis was diagnosed. Symptoms resolved within minutes of angioedema-challenged oral ingestion of diphenhydramine capsules, the only available HIRA. Many food, chemical, and environmental triggers were identified. More symptoms emerged: tinnitus, blurred vision, cough, bloating, vomiting, diarrhea alternating with constipation, rapid weight fluctuations, migratory pruritic rash and edema and hives, dermatographism, dyshydrotic eczema, and Raynaud's phenomenon. Episodes often went untreated as diphenhydramine sedation and epinephrine impeded work.

In September 2011, she returned home. Somatism was suspected; requests for epinephrine and allergy referral were denied. Syncopes and anaphylaxes went untreated. At allergy evaluation in December 2011, serum tryptase and immunoglobulin E were normal. Skin testing reacted to

many environmental antigens but few foods. Non-sedating HIRAs and montelukast proved unhelpful. A hematologist found consistently elevated urinary N-methylhistamine (81 and 225 mcg per gram of creatinine, normal 0–65) and, off proton pump inhibitors, serum chromogranin A (8 and 6 ng/mL, normal 0–5). Tryptase, anti-nuclear antibody, functional C1 esterase inhibitor, urinary 5-hydroxy-indole-acetic-acid, and blood counts and smears were normal. Marrow was histologically and molecularly negative for MC disease. Esophagogastroduodenoscopy in October 2012 found esophageal and antral erythema; biopsies initially appeared normal (Fig. 1), including negative examinations for various infections.

Mast cell activation syndrome was diagnosed (1). Previously tried drugs were retried, to no avail. Other medications proved intolerable. Finally, imatinib (200 mg/d) stopped her spontaneous anaphylaxes, but only for a few months.

In late 2013, on her own, she obtained partial genomic sequencing from saliva. Using Internet resources, she interpreted a single nucleotide polymorphism as indicative of homozygous KIT-F584C mutation, predicted imatinib-resistant but sunitinib-sensitive (3). Imatinib was replaced with low-dose sunitinib (12.5 mg once daily) in April 2014. Complete remission emerged in 24 h and has been sustained 13.5 months with no clinical or laboratory toxicities. She suffered no more anaphylaxes (even upon trigger exposures), stopped her other medications, and resumed full activities. Physical examination normalized. Professional analysis of her sequencing found no KIT-F584C mutation but a variety of mostly intronic SNPs and indels in several genes, including KIT, associated with immune and neoplastic diseases (Data S1). We sequenced KIT from her peripheral blood MC DNA [protocol referenced in (2)] and found no mutations.

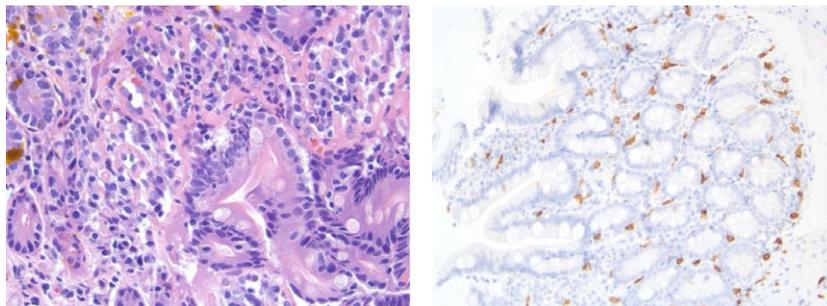


Figure 1 Occult nature of mast cells (MCs) in routine pathologic review. Routine staining of patient's endoscopic duodenal biopsy with hematoxylin and eosin (H&E) (left, 20 \times) was interpreted as normal, while CD117 staining (right, 20 \times) readily revealed a number of MCs not identifiable as such on H&E staining. Even though the MCs in the CD117-stained biopsy numbered only 10–15 per high power field (40 \times), considered within normal limits, this pair of views illustrates the importance of performing CD117 staining if MC disease is suspected. CD117 targets the extracellular domain of transmembrane tyrosine kinase KIT, the dominant MC regulatory element. As KIT is expressed approximately 10-fold more in MCs than any other human cells, bright CD117-staining cells likely are MCs. Other stains targeting MC granules or their contents (e.g. tryptase, Giemsa, toluidine blue, Alcian blue) may not reliably identify partially or wholly degranulated MCs in MC activation disease.

Discussion

Effective treatments for aggressive MC disease are few; our experience suggests sunitinib may add to this armamentarium.

Onset and escalation of symptoms in MCAS often follow stress or novel antigenic exposure (1). Misdiagnosis as somatism is common.

Mutational heterogeneity augurs therapeutic heterogeneity. Therapeutic failure prompts reconsideration of diagnosis, but further therapeutic efforts are warranted if no better diagnosis is identified.

Different TKIs differentially inhibit different KIT mutants (3). Rajasekran and Rao found F584C predicted, *in vitro*, imatinib resistance and sunitinib sensitivity (3).

Imatinib has been used in SM (typically, rare cases without KIT codon 816 mutation). Imatinib is the only TKI yet reported tried in MCAS; all reported successes have been at 200 mg/d.

Our patient's loss of imatinib response might have been due to emerging reactivity to imatinib (or accompanying excipients) or to resistance from subclonal evolution, inhibiting imatinib binding (as seen sometimes in GIST), which multi-TK-targeted sunitinib was designed to counter (4). Multitargeting may explain sunitinib's utility here as we could not confirm any KIT mutations. Sunitinib also binds to PDGFR- α , PDGFR- β , VEGFR1, VEGFR2, VEGFR3, FLT3, CSF-1R, and RET, some of which are MC-expressed. Sunitinib treats imatinib-resistant GIST but also reduces MC degranulation in murine oral allergy syndrome (5). More research may clarify a role for sunitinib in MCAD.

Finally, in spite of doors possibly serendipitously opened here, we note hazards in providing complex results to insufficiently counseled patients. Direct-to-consumer testing services may be increasingly obligated to minimize this risk, especially given average U.S. reading ability at eighth-grade level.

Acknowledgement

The authors wish to thank hematopathologist Gail Bentley, M.D. (Oncometrix, Memphis, TN) for providing the photomicrographs shown in Fig. 1.

Support

No funding or other support was received for this work from any source.

Competing interests

None. Dr. Afrin was an informal consultant on the case, conceived of the article, and was the principal author. Dr. Patel was personally involved in the care of the patient. Dr. Cichocki performed mast cell isolation and KIT sequencing. Dr. Molderings analyzed commercial genomic sequencing results. All authors reviewed, edited, and approved the article.

Author information

LBA is an Associate Professor of Medicine in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota, Minneapolis, MN, USA. FC is an Assistant Professor of Medicine in the Division of Hematology, Oncology, and Transplantation at the University of Minnesota, Minneapolis, MN, USA. KP is in private oncology practice in Little Rock, AR. GJM is an Associate Professor of Medicine and Senior Researcher in Mast Cell Diseases at the Institute for Human Genetics, University of Bonn, Germany.

References

1. Afrin LB. The presentation, diagnosis and treatment of mast cell activation syndrome. *Curr Allergy Clin Immunol* 2014;**27**:146–58.
2. Molderings GJ. The genetic basis of mast cell activation disease. *Crit Rev Oncol Hematol* 2015;**93**:75–89.
3. Rajasekaran R, Rao S. Exploring the cause of drug resistance by the detrimental missense mutations in KIT receptor: computational approach. *Amino Acids* 2010;**39**:651–60.
4. Ashman LK, Griffith R. Therapeutic targeting of c-KIT in cancer. *Expert Opin Investig Drugs* 2013;**22**:103–15.
5. Yamaki K, Yoshino S. Tyrosine kinase inhibitor sunitinib relieves systemic and oral antigen-induced anaphylaxes in mice. *Allergy* 2012;**67**:114–22.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Genetic alterations found in patient's commercial partial genomic sequencing. Mutations which have been reported in the literature to be strongly associated with immune and neoplastic diseases are shaded red.