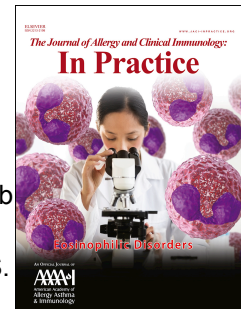


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Systemic mastocytosis with an associated hematologic neoplasm complicated by recurrent anaphylaxis: prompt resolution of anaphylaxis with the addition of avapritinib

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47 Clinical implications

48 We present a case report of systemic mastocytosis with an associated hematologic neoplasm
49 (SM-AHN) initially managed on multiple medications including the kinase inhibitor midostaurin
50 who developed recurrent, serious episodes of anaphylaxis that promptly ceased after starting
51 avapritinib.

Case report

Systemic mastocytosis (SM) is a myeloid neoplastic condition typically associated with a D816V gain-of-function mutation in KIT and is characterized by pathologic over-proliferation and activation of mast cells. We present the case of a 69-year-old male with SM with an associated hematologic neoplasm (SM-AHN), namely myelodysplastic syndrome (MDS), whose course was complicated by multiple anaphylaxis episodes. Strikingly, these episodes ceased shortly after the addition of avapritinib.

The patient presented to the emergency department six times over eight months with episodes of acute, unprovoked chest pain, shortness of breath, hypotension, wheezing, vomiting and diaphoresis. In five of the six, he was admitted to the cardiac intensive care unit (ICU) including one episode of cardiac arrest necessitating cardiopulmonary resuscitation. During one of these admissions, cardiac catheterization revealed severe myocardial bridging prompting a myocardial unroofing procedure. Post procedurally, (Day -480, Figure 1) the patient developed shock of unclear etiology. Workup revealed a tryptase level of 143 ng/mL (Figure 1) and a non-pruritic rash on his abdomen and thighs. Bone marrow biopsy showed SM involving 5% of a hypercellular bone marrow (70%), ringed sideroblasts, and occasional scattered spindle-shaped tryptase-positive cells in clusters co-expressing CD25. Bone marrow aspirate was positive for KIT D816V. A diagnosis of SM-AHN was made after a sequencing panel confirmed the KIT D816V mutation and also detected a mutation in the *SF3B1* gene which is seen in myelodysplastic syndrome (MDS). Medications at the time of discharge included cetirizine 20 mg twice daily (BID), montelukast 10 mg daily, aspirin 81 mg daily, and ranitidine 150 mg BID.

The patient did well for 15 months on these therapies before developing worsening flushing, lightheadedness, dyspnea, diaphoresis, nausea, diarrhea, vomiting, chest pain, tingling of the extremities, and hypotension leading to three community hospital emergency department visits. He was started on midostaurin 50 mg BID on day -54. However, in the three weeks preceding hospitalization, despite escalation of daily prophylactic medications including oral cromolyn sodium 200 mg four times daily (QID), cetirizine 20 mg BID, aspirin 81mg daily, and montelukast 10 mg daily, he experienced at least 13 outpatient episodes of unprovoked anaphylaxis requiring multiple epinephrine auto-injector doses which subsequently led to a 39-day hospitalization (Figure 1). Although several inpatient episodes were associated with hypotension and acute hypoxemic respiratory failure, each episode promptly resolved following administration of epinephrine and IV diphenhydramine. Serum tryptase levels transiently increased on multiple occasions (Figure 1). Repeat bone marrow biopsy on hospital day (HD) 12 demonstrated increased mast cell burden affecting 50% of a hypercellular bone marrow (90% cellularity) with scattered, large mast cell aggregates and changes consistent with known MDS. The bone marrow aspirate showed increased mast cells (8%) and fluorescence in situ hybridization analysis for various gene rearrangements, platelet-derived growth factor (PDGFR)-A, PDGFR-B and fibroblast growth factor receptor 1, were negative. These findings confirmed diagnosis of SM-AHN rather than aggressive SM or mast cell leukemia.

During this hospitalization, the patient received 28 doses of epinephrine and had two ICU stays for hypoxemia and hypotension. He briefly required an epinephrine drip due to recurrent anaphylaxis despite further escalation of prophylactic medications including cromolyn sodium 200 mg QID, ketotifen 10mg daily, diphenhydramine 50mg every four hours, aspirin 650 mg

three times daily, famotidine 40 mg BID, montelukast 20 mg BID, a five-day course of methylprednisolone 50 mg (HD 22-27) and one dose of omalizumab 300 mg (HD 6). Due to continuing episodes of anaphylaxis, midostaurin was discontinued on HD 24 and compassionate-use avapritinib was started at 200 mg daily on HD 29. He was monitored inpatient for an additional 10 days, during which time he had no further episodes of anaphylaxis. The patient was discharged home on avapritinib 200 mg daily along with multiple preventive medications (Figure 1).

The patient was weaned off of aspirin and ketotifen over the next two months. His random tryptase levels initially declined, reaching a nadir of 237 ng/mL but then began rising (Figure 1) although he has had no further episodes of anaphylaxis. One year out from hospitalization, he remains on avapritinib 100 mg/200 mg alternating daily dosing, cetirizine 20 mg daily, famotidine 40 mg BID, cromolyn sodium 200 mg QID, fexofenadine 360 mg daily, and montelukast 10 mg daily despite rising tryptase levels to 1,210 ng/mL. Remarkably, even with rising tryptase levels and presumably increasing mast cell burden, he has had no further episodes of anaphylaxis.

We report an unusual case of SM-AHN complicated by multiple, refractory, well-documented episodes of anaphylaxis despite aggressive pharmacotherapy including midostaurin, a drug approved for the treatment of adults with aggressive SM, SM-AHN, or mast cell leukemia.

This patient's recurrent anaphylaxis promptly resolved with avapritinib, an oral type I multi-kinase inhibitor with potent and selective activity against KIT D816V and PDGFRA A-loop

mutants. This drug was specifically designed to have activity against the D816V KIT mutation, binding KIT D816V roughly 10 times more avidly than midostaurin (1-3). It is currently approved for the treatment of certain gastrointestinal stromal tumors carrying PDGFRA exon 18 mutations. Although still under investigation for SM (NCT03731260), it remains to be seen if the effect on anaphylaxis is generalizable to this population (4). How its use in our patient resulted in complete cessation of his recurrent anaphylaxis remains unclear. Avapritinib does not appear to target other kinases such as spleen associated tyrosine kinase (Syk) and Bruton's tyrosine kinase (BTK) based on published pharmacology data (5, 6). This patient had SM-AHN with a second mutation in *SF3B1* that affects hematopoietic cell growth and differentiation but is not known to impact mast cell secretory responses. Avapritinib is recognized to have multiple side effects, many of which our patient experienced including cognitive dysfunction, fatigue, lower extremity and periorbital edema, ultimately requiring dose reduction from the initial 200mg daily. Additionally, other adverse effects seen at higher doses of avapritinib include intracranial hemorrhage, more commonly observed with low platelets, and severe myelosuppression; neither of these was seen in our patient. Regardless, our case report adds to the limited body of literature describing the use of and clinical responses to avapritinib.

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160 Figure legend

161 Figure 1 Tryptase levels, significant clinical events and medications given.

162 Circle: epinephrine and diphenhydramine given, number in circle indicates doses of epinephrine

163 X: diphenhydramine

164 Triangle: omalizumab single dose

165 *: 3 ED visits requiring epinephrine and/or diphenhydramine, 2 episodes requiring

166 diphenhydramine alone over 5 months

167 S: steroids

168 R: ranitidine

Figure 1: Tryptase levels, controller medications and clinical events

