

Case Report: Unusual Manifestation of KIT Negative Systemic Mastocytosis

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Abstract

Aggressive systemic mastocytosis is a rare hematologic neoplastic disease that presents with a poor prognosis and low survival rate. It typically manifests with symptoms associated with mast cell release of bioactive substances, causing anaphylaxis, flushing, autonomic and hemodynamic instability, gastric distress, and headache. Moreover, more than 95% of cases are related to a mutation in codon 816 of the *KIT* gene, located on human chromosome 4q12 which codes for a type III receptor tyrosine kinase. We present a 78-year-old Hispanic man diagnosed with the aggressive subtype of systemic mastocytosis, who had an atypical manifestation and a KIT-negative variant. The diagnosis was confirmed based on pathologic and serologic findings which included mast cell infiltration of the spleen and bone marrow, malignant ascites, and an unusually elevated serum tryptase.

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Introduction

Systemic mastocytosis (SM) is one of the seven myeloproliferative neoplasms (MPN) classified by the WHO 2008. The other six disorders are chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), polycythemia vera (PV), primary myelofibrosis (PM), essential thrombocythemia (ET), and chronic eosinophilic leukemia (CEL).¹ SM is a rare, somatic disorder, characterized by an abnormal expansion and accumulation of neoplastic mast cells (MCs) in various organ systems.² Depending on the extent of organ involvement, SM can be divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumors. CM has skin-limited involvement and occurs most commonly in the pediatric population. Localized MC tumors consist of MC conglomerates that form either an MC sarcoma or an extracutaneous mastocytoma, depending on the involved tissues. SM is characterized by mast cell infiltration with more than one organ system, which may include spleen, GI tract, and bone marrow.²

SM is further classified into five subtypes: indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic non-MC-lineage disease (SM-AHNMD), aggressive SM (ASM), and mast cell leukemia (MCL). These last three subtypes have poor prognosis. Symptoms of SM are caused by mass effect by the neoplastic mast cells, and the release of bioactive substances acting at both local and distal sites. One of these substances is tryptase, which may cause anaphylaxis, flushing, palpitations, vascular collapse, gastric distress, lower abdominal cramping pain, and recurrent headache.³ Other features of aggressive SM may include pancytopenia, lymphadenopathy, hypoalbuminemia, malabsorption, or large osteolyses (possibly as a result of mast cell-mediated fibrotic changes in these organs) as well as hepatosplenomegaly and ascites due to periportal fibrosis associated with mast cell infiltration of liver parenchyma. The advanced variants of SM have poor prognosis, with an overall survival of less than 12 months.²

Case Presentation

A 78-year-old Hispanic man with arterial hypertension, controlled diabetes mellitus type II, chronic atrial fibrillation, coronary artery disease, and colonic diverticulosis was sent for consultation to the hematology-oncology section in August 2011 because of the incidental discovery of normocytic anemia with thrombocytopenia (white blood cell [WBC] 4.5, hemoglobin [Hgb] 11.1, mean corpuscular volume [MCV] 94.9, $84 \times 10^3/\text{microL}$ platelets—40 segmental neutrophils, 38 lymphocytes, and 20 monocytes). The patient reported taking warfarin, atenolol, and lisinopril. He also denied the use of alcohol or smoking and revealed pertinent family history of two siblings with colon cancer. There was an absence of splenomegaly, lymphadenopathy, or ascites. An anemia workup revealed normal levels of B12, folate, iron, and ferritin levels.

A bone marrow biopsy revealed 80% cellularity with dysmegakaryopoiesis and slight monocytosis, suggestive of MDS. Cytogenetic results were normal. Because the patient had mild anemia and no symptoms with a low-risk score, he continued to be observed with no requirement of transfusions or active treatment. In 2013, the patient had a follow-up colonoscopy with diverticuli and a sessile benign rectal polyp. However, in

a follow-up examination in July 2015, the patient developed early satiety and exhibited a 13-pound weight loss 3 months prior to evaluation. On physical examination, he had epigastric pain upon palpation. It was recommended that he undergo an upper endoscopy. The endoscopy revealed mucosal erythema in the gastric area and a clean base ulcer; biopsy showed active chronic gastritis and the presence of *Helicobacter pylori* requiring treatment with amoxicillin and clarithromycin for 2 weeks.

Follow-up laboratory tests revealed WBC 4.1 (29 segmental neutrophils, 38 lymphocytes, 23 monocytes, 8 eosinophils); Hgb of 9.3, hematocrit (Htc) of 30.1, and a platelet count of 75,000. Blood chemistry was significant for alkaline phosphatase in 315 U/L (normal results range 30-115 U/L), but BUN, creatinine, and electrolytes were within normal ranges. Urinalysis, hepatitis B and C panel, thyroid function tests, and the HIV test were non-contributory.

In the setting of constitutional symptoms and weight loss with worsening anemia, an abdominopelvic computed tomography (CT) scan was performed. Abdominal CT showed diffuse lymphadenopathy, which was absent in previous imaging studies taken in 2010. Skeletal bone revealed heterogeneous densities suggesting diffuse sclerotic metastatic disease versus MPN. Additional findings included hepatocellular disease (hepatic nodular contour but no discrete enhancing lesions), pelvic ascites, and a left-sided pleural effusion with rounded atelectasis. A PET/CT scan disclosed a possible mild hypermetabolic borderline size spleen (SUV 3.2) and skeletal bone marrow. There was no increased captation in abdominal lymphadenopathy (largest 2.4 cm). Based on the findings reported, a spleen biopsy was performed by an interventional radiologist. Pathology reports revealed fibrosis with increased eosinophilic, monocytoid cell infiltrate, and hyalinized granulomas as well as spindled cell areas positive for mast cell tryptase, CD117 and CD68, but negative for CD2, S100, AE1/3, CD34, CD163, CD21, and CD31. Tissue was negative for blasts, Hodgkin cells, CD20, CD3, CD34, CD15, and CD30 markers. Acid fast bacilli and Grocott's methenamine silver stains were also negative. The pathology was reviewed by the Joint Pathology Center which agreed that the morphology of spindle cell areas together with the phenotype were consistent with a diagnosis of mast cell disease (Figures 1 and 2). A bone marrow aspirate and biopsy also disclosed clusters of spindle cells, positive for CD117 and tryptase confirming the diagnosis of systemic mastocytosis. Cytogenetics were normal, and there were no mutations in *JAK2* or *c-KIT* (D816V

FIGURES 1 & 2. Needle core biopsy of the spleen shows eosinophilic infiltrate as well as atypical mast cells with clear cytoplasm and somewhat spindle cell morphology. These cells were positive for CD117 and tryptase (mast cell markers).

FIGURE 1.

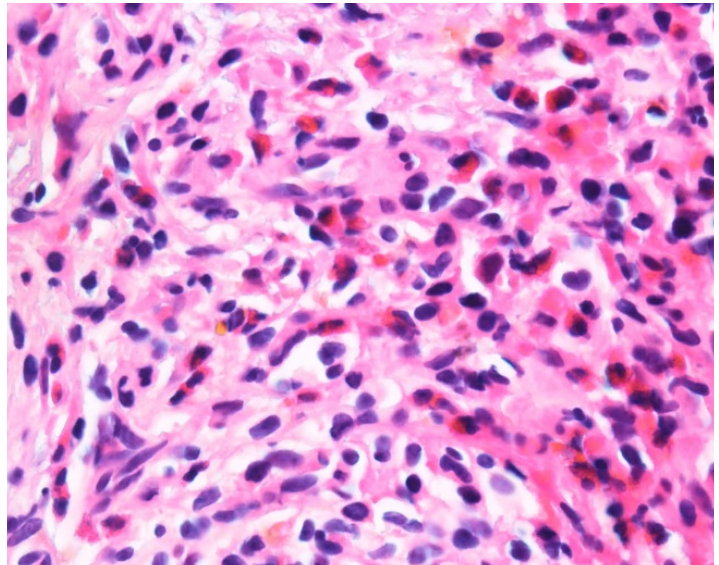
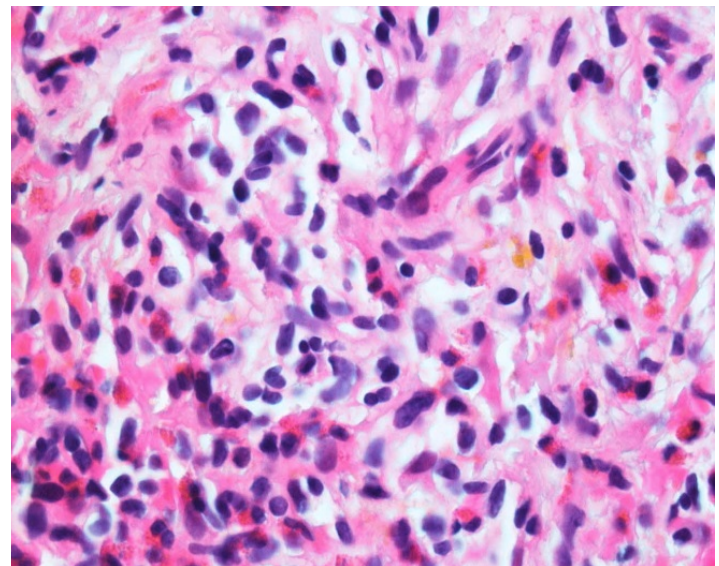


FIGURE 2.



codon) by FISH. Serum tryptase levels were 165 ng/ml (NV 2-10).

The patient was started on oral imatinib 400 mg, as indicated for the treatment of adult patients with aggressive systemic mastocytosis without the D816V *c-KIT* mutation or with unknown *c-KIT* mutational status.⁴ Alternatives, such as interferon or 2-CDA were discussed, but the patient was

initially considered too fragile to tolerate those alternatives. Patient evolved with progressive tension ascites and worsening anemia (6.3 gm/dl) requiring PRBC transfusions. The patient had poor tolerance to imatinib, even at a lower dose of 100 mg due to worsening diarrhea and tension ascites, requiring an intraperitoneal catheter for chronic drainage.

During the following months, the patient was hospitalized on multiple occasions due to massive ascites and symptomatic anemia. Low-dose prednisone at 5 mg improved the platelet count to over $150 \times 10^3/\text{microL}$. Due to poor clinical response to imatinib, the patient had a trial of low-dose interferon alpha (1 million units) delivered subcutaneously, three times a week. His aggressive mastocytosis progressed. The patient died in June 2016 in hospice care.

Discussion

Uncommitted and MC-committed progenitors express KIT, a type III receptor tyrosine kinase encoded by a 21-exon containing gene located on human chromosome 4q12.⁴ The ligand of the KIT receptor, stem cell factor (SCF), initiates the development of MCs from their uncommitted and MC-committed precursor cells as well as the proliferation, maturation, survival, and proinflammatory mediator release from MCs.^{5,6} In mastocytosis, more than 95% of cases undergo SCF-independent differentiation and accumulation of MCs due to a KIT receptor tyrosine kinase gain-of-function mutation (D816V). This is characterized primarily as an aspartic acid to valine substitution, which results in uncontrolled proliferation, enhanced survival and cell autonomous growth of MCs.² This mutation is often detectable independent of the category of SM, including most aggressive subtypes of SM. Our patient, however, tested negative for this mutation, further emphasizing the uniqueness of this case. Additional somatic mutations are found in patients with SM-AHNMD, ASM, and MCL. These include mutations in *TET2*, *SRSF2*, *ASXL1*, *CBL*, *RUNX1*, and *RAS*.^{7,9}

The diagnosis of SM is based on pathologic and laboratory findings. Several criteria have to be met in order to confirm the diagnosis. Criteria are divided into minor and major criteria. When one major and one minor or three minor criteria are detected, a diagnosis can be established. Minor criteria are: (1) MCs in bone marrow (BM) infiltrates, infiltrates in another extracutaneous organ, or in a BM smear showing spindle-shaped morphology (2) *KIT* mutation at codon 816 in extracutaneous organs (3) BM MCs express CD2 and/or CD25 by flow or IHC, (4) Serum total tryptase $>20 \text{ ng/mL}$. Major criteria are multifocal dense infiltrates of MCs in BM sections or other extracutaneous organ(s) (>15 MCs in aggregate).¹

This patient complies with the major criteria, as multifocal dense infiltrates of mast cells were identified both in bone marrow and spleen. He also complies with the minor criteria of

a total serum tryptase $>20 \text{ ng/mL}$. Since other flushing disorders were excluded, including carcinoid tumor and pheochromocytoma, this patient was diagnosed with SM.

The aim of initial management is to reduce the burden of systemic mediators of inflammation. H1 antihistamine is usually prescribed for flushing and pruritus in ASM patients. This patient, however, did not exhibit such symptoms. Instead, H2 antihistamine or proton pump inhibitor for gastric acid hypersecretion and oral cromolyn sodium for diarrhea and abdominal pain was prescribed, as well as, aspirin for severe flushing to block biosynthesis of PGD2. Systemic glucocorticoids appeared to alleviate the malabsorption. The patient had improvement in diarrhea with cromolyn sodium.

In terms of management of ASM itself, interferon alpha (as long-term subcutaneous therapy) or cladribine (2CdA, 3-6 cycles) are first-line therapy for patients who can tolerate it. If ASM is rapidly progressing, more intensive therapy is required. Polychemotherapy with fludarabine or 2CdA, often in combination with cytosine arabinoside is also an option for these patients. In older patients and those who cannot tolerate intensive therapy, conventional cytoreductive agents (ie, 2CdA) or palliative drugs (ie, hydroxyurea [HU]) may be prescribed. In cases in which intensive therapy cannot be offered, palliative therapy with HU is an option.² A recent open-label study demonstrated efficacy of midostaurin, an oral small molecule agent, which inhibits multiple kinases in patients with advanced systemic mastocytosis, with a response rate of 60%.¹⁰ It is an emerging therapeutic option that inhibits non-mutant and mutant *KIT D816V*.

Despite treatment with two lines of therapy, imatinib and interferon, the patient continued with progressive ascites and worsening functional status.

Conclusion

Mastocytosis is a rare hematologic disease that requires clinical suspicion and pathologic expertise. In this case report, treatment of advanced SM is a challenge, and most patients relapse or have resistant disease. There is hope that novel agents, especially tyrosine kinase inhibitors that can target the *KIT* mutations can alter the dim prognosis of these patients.¹⁰ For patients that have drug resistance and are young and fit, stem cell transplant is an alternative treatment option.¹¹ Treatment for SM has to be adjusted to the individual patient and the SM category. In indolent disease, the main aim is to control mediator secretion and in aggressive disease, the aim is to suppress malignant clone expansion.

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