

Systemic Mastocytosis Masquerading as Metastatic Breast Carcinoma

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The Case

A 70-year-old female was diagnosed in October 1998 with a mammographically detected breast cancer that on biopsy was high grade, estrogen receptor positive, progesterone receptor equivocal, and *HER2/neu* negative by immunohistochemistry. A lumpectomy showed the tumor to be 1.8 cm with negative margins. On axillary lymph node dissection, none of 18 nodes were involved. The patient underwent postoperative breast irradiation then started treatment with tamoxifen. After a spontaneous upper-extremity deep venous thrombosis, she was switched to adjuvant hormonal therapy with anastrozole (Arimidex, AstraZeneca). The patient developed a rash while on anastrozole and was switched back to tamoxifen along with anticoagulation. She completed 5 years of therapy in November 2003.

Work-up for elevated liver function tests (LFTs) led to a computed tomography scan of the abdomen and pelvis. The liver was unremarkable, but diffuse sclerotic lesions were seen throughout the visualized axial skeleton and subsequently confirmed on plain films. Both magnetic resonance imaging (MRI) and positron emission tomography scans of the spine were unrevealing as to distant metastases or uptake in the spine. A bone scan was also negative for skeletal uptake. The patient was referred to our institution in January 2004.

At our institution, a repeat MRI of the thoracic and lumbar spine showed minimal compression fractures at T2, T4, T11, L3, and L4 along with diffuse hypointensity throughout the visualized marrow. Work-up of elevated LFTs ultimately revealed primary biliary cirrhosis with no evidence of a neoplastic process. A bone marrow aspirate and biopsy were performed in an effort to diagnose metastatic breast cancer.

The bone marrow instead showed increased cellularity (70%) with an increase in spindle-shaped mast cells. Fibrosis (4+) was noted in the vicinity of the spindle-shaped mast cells, whereas the remaining bone marrow had minimal (1+) fibrosis. Also noted was an atypical myelodysplastic/myeloproliferative disorder (MDS/MPS) with large, atypical monocytes and small, atypical megakaryocytes. Immunohistochemical studies revealed that the spindle-shaped cells were positive for c-kit and tryptase. Chromosomes were 46, XX in 20 of 20 metaphases. Serum tryptase was then checked and noted

to be 157 ng/mL (the normal level is less than 11.5 ng/mL). Peripheral blood and bone marrow eosinophil and basophil counts were normal. There was no evidence of breast cancer.

Upon further questioning, the patient had no symptoms of flushing, diarrhea, dermatographism, urticaria, hives, wheezing, or dyspepsia. There was no evidence in the peripheral blood of a myelodysplastic or myeloproliferative disorder.

Further testing of the bone marrow specimen was performed. Fluorescence in-situ hybridization (FISH) studies showed that 2.5% of 200 nuclei had 1 *CHIC2* and 2 fibroblast growth factor receptor 3 signals, and 0% of 200 nuclei had 3 *Fip1-like 1* (*FIL1L1*)/platelet-derived growth factor receptor α (*PDGFRA*) fusion signals (both results were normal).

Discussion

Systemic mastocytosis (SM) is characterized by infiltration of tissue by neoplastic mast cells. It is important to separate SM from the skin-limited cutaneous mastocytosis. In this disorder, the mast cells invade various tissues, including bone marrow, liver, spleen, and skin. Clinical disease results from invasion of the organs and can include bone pain, pathologic fractures, cytopenias, rash, and other adverse events.¹ Symptoms can result also from mast cell degranulation causing urticaria, hypotension, nausea, diarrhea, flushing, and even anaphylaxis.²

Diagnosis relies primarily on a high clinical suspicion. Serum tryptase is often elevated in these disorders. Ultimately, a biopsy, often of the bone marrow, is needed to confirm disease. Bone marrow examination often shows clusters of fusiform mast cells that stain positive for tryptase and CD117. Bone marrow specimens should also be examined for coexisting hematologic disorders (especially MDS/MPS), eosinophilia, and reticulin fibrosis which frequently coexist.^{2,3}

Activating mutations of c-kit are frequently noted, most commonly Asp816Val. This amino acid substitution of c-kit causes activation of the enzyme on the cell surface.⁴ In SM with eosinophilia (SM-eo) there is frequently a tyrosine kinase created by fusion of *PDGFRA* and *FIL1L1* genes. Both of these genes are located on chromosomes 4q12, and this gene product can result from an interstitial chromosomal deletion on chromosome 4q12. A surrogate marker for this gene fusion is the *CHIC2* deletion, which represents the deleted chromosomal material. A FISH assay can determine this deletion in patients with SM-eo.⁵

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After a diagnosis of SM, the patient's course can be classified into 1 of 4 subtypes: indolent (no end-organ dysfunction), aggressive (end-organ dysfunction including cytopenias, hepatosplenomegaly, bone disease), SM associated with another (usually myeloid) hematological disorder (SM-AHD), and the very rare mast cell leukemia/sarcoma. Most patients have indolent disease with SM-AHD being the next most common.^{6,7}

Treatment first involves agents aimed at mitigating the effects of mast cell degranulation. This can include avoiding exacerbating factors (hot showers, physical trauma, etc), appropriate anesthesia care, antihistamines, cromolyn sodium, carrying an epinephrine injection (EpiPen, Meridian), appropriate corticosteroid preparations, and wearing a medical alert bracelet.²

For patients with end-organ damage from mast cell tissue infiltration, cytoreductive therapy is indicated. Patients with SM-*eo* (PDGFRA-FIP1L1 fusion gene product) show remarkable sensitivity to low-dose (100 mg/day) imatinib mesylate (Gleevec, Novartis). Patients without expression of this gene product and those with the more common Asp816Val substitution do not respond to imatinib mesylate.^{5,8} Typical therapies for these patients include interferon- α and cladribine (Leustatin, Ortho Biotech). Interferon- α has been shown to be beneficial in some reports, but not uniformly so, and is often difficult to tolerate.⁹⁻¹¹ Cladribine is often used in patients with interferon- α -refractory or -intolerant disease.^{12,13}

The Patient

This particular patient had no symptoms of increased mast cell degranulation despite her increased serum tryptase. Other than the bony involvement, she had no evidence of skin or visceral tissue invasion. We elected to treat her with oral bisphosphonates, calcium, and vitamin D and then reassess. At follow-up 7 months after her diagnosis, she was stable symptomatically with no clear evidence of mast cell degranulation symptoms or further organ infiltration. She was maintained on the same treatment.

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Review

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Mastocytoses (“mast cell diseases”) are bone-marrow–derived hematologic disorders comprising various subcategories with extremely different clinical features and prognosis. An updated classification of these rare diseases has been widely accepted and is included in the World Health Organization book on hematologic malignancies.^{1,2} The separation of the purely cutaneous forms of mastocytosis (urticaria pigmentosa) with a generally excellent prognosis from the systemic variants (including the extremely rare mast cell leukemia) is of major clinical importance. Usually, the diagnosis of SM is based on the histomorphologic evaluation of a bone marrow trephine biopsy specimen.

The introduction of defined diagnostic criteria enables assessment of tissue involvement by mastocytosis in most of the cases.¹ The histopathologist plays a crucial role in establishing a diagnosis of mastocytosis because the only major criterion is the demonstration of at least 1 compact dense infiltrate consisting of at least 10–15 mast cells. It was proposed that only the combination of the major with 1 minor criterion (or, when the major criterion is missed, 3 of 4 minor criteria) enables the diagnosis of mastocytosis to be established definitively. Minor diagnostic criteria comprise prominent spindling of mast cells (which is regarded as cytologic atypia), expression of aberrant markers, in particular the T-cell–associated antigens CD2 and/or CD25 (which are not expressed on normal/reactive mast cells), demonstration of the activating point mutation D816V of the c-kit proto-oncogene, and a persistently elevated serum tryptase level (>15 ng/mL).^{1,3}

Regarding the interesting report by Huber and Ayalew describing a case of SM initially presenting with disseminated osteosclerotic lesions and thereby mimicking metastatic breast cancer, 2 major points deserve further discussion. First, do the presented criteria fulfill the standards for a diagnosis of mastocytosis to be made, and if so, what subcategory of disease should be favored? Second, is the association of mastocytosis with metastatic carcinoma a mere coincidence of 2 neoplastic diseases or does it show that patients with mastocytosis may have a tendency to develop a synchronous or metachronous malignancy?

Huber and Ayalew clearly show an increase in spindle-shaped bone marrow mast cells and a markedly elevated serum tryptase of 157 ng/mL. However, they describe neither the

presence of multifocal dense or compact mast cell infiltrates nor the immunohistochemical demonstration of an atypical expression of CD25 by mast cells. In addition, the presence of an activating point mutation of c-kit (usually, D816V) is not mentioned. Altogether, only 2 minor diagnostic criteria are clearly stated by the authors. A diagnosis of mastocytosis thus cannot be made with certainty. However, it is very likely that compact mast cell infiltrates were present in the bone marrow of the patient, although a precise description is not given in the text. Moreover, the bone marrow features with marked hypercellularity and atypia of monocytes and megakaryocytes make it very likely that the present case should be properly classified as systemic mastocytosis with an associated clonal non–mast-cell lineage hematologic disorder (SM-AHNMD), apparently of SM-MDS/MPS type. Among associated hematologic diseases, MDS/MPS, formerly widely known as chronic myelomonocytic leukemia, are the most common, followed by acute myeloid leukemias, whereas malignant lymphoproliferative diseases are rarely encountered.^{4,5}

There is the question whether or not patients with mastocytosis show also an increased risk to develop solid cancers. It seems that patients with SM not only have a tendency to develop hematological malignancies (SM-AHNMD) but also have an increased incidence of solid cancers. Travis et al⁶ analyzed 60 patients with systemic mastocytosis and found 11 AHNMDs and 8 solid cancers. It seems of interest that the occurrence of associated hematologic and solid malignancies in such patients is seen usually before or within 12 months after a diagnosis of SM has been established.⁶

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