Dasatinib-Responsive Mast Cell Neoplasms As Initial Presentation of Chronic Myelogenous Leukemia in Blast Phase

Case Report

A 50-year-old man presented with a 3-month history of left supraorbital mass, left leg pain, and walking difficulty; he denied symptoms of flushes, diarrhea, or syncope. On physical examination, the patient had a 2-cm firm, nontender mass centered at the junction of the left lateral and superior orbital walls. Patient did not have lymphadenopathy or organomegaly. The patient was a 30 pack per year smoker, and his medical history was not relevant. On admission, his WBC count was $8.7 \times 10^9/L$; hemoglobin, 11.7 g/dL; and platelets, $370 \times 10^9/L$. A peripheral blood cell differential was normal. Lactate dehydrogenase was normal, and tryptase level was slightly increased at 12.8 ng/dL. Radiologic studies revealed a lytic lesion involving the superior and lateral orbital walls (Fig 1), multiple lytic lesions in the left pelvis and left scapula, and a pathologic fracture of the left femoral head. Biopsies of the orbit, left femoral head lesion, and random iliac crest bone marrow were performed.

Pathologic and cytogenetic findings. Excision of the left orbital mass showed an atypical mononuclear cell infiltrate with abundant eosinophils. The mononuclear cells showed scant to moderate cytoplasm with pale, coarse basophilic granules, which were better appreciated on a significant proportion of cells on touch imprints (Fig 2). These cells were strongly positive for CD117 and weakly positive for tryptase; approximately 15% were CD34+.

Biopsy of the left femur pathologic fracture revealed sheets of mononuclear cells, with focal tumor necrosis and stromal fibrosis. Similar to the mononuclear cells in the supraorbital mass, the mononuclear cells of the left femur contained basophilic and azurophilic granules, but the nuclei in the femur were oval to bilobed. Compared with the mononuclear cells of the orbital mass, the mononuclear cells of the femur were not only strongly positive for CD117 but also strongly positive for tryptase and negative for CD34.

Fig 2.

Patches of relatively uninvolved areas in femur biopsy showed trilineage hematopoiesis, with no increase in CD34+ cells. A bone marrow core biopsy from the iliac crest showed large areas of fibrosis (> 50%) with large clusters of perivascular mononuclear cells. These cells were CD117+ and tryptase negative. The background hematopoietic cells showed 2% blasts, 12% myelocytes, 31% metamyelocytes/bands/neutrophils, 8% eosinophils, 8% basophilic cells, 1% monocytes, 17% lymphocytes, and 21% normoblasts.

Flow cytometry immunophenotyping performed on bone marrow samples revealed many CD117+ cells with a low side scatter and located at the basophil area by CD45/side scatter. Expression of CD59, CD63, and CD69 in these bone marrow cells was lower than that typically seen in systemic mast cell disease, although the abnormal cells showed aberrant coexpression of CD25. The orbital mass contained an immature cellular population (CD45 dim, partial CD34) with CD117 and CD25 coexpression, and the expression patterns of CD59, CD63, and CD69 were similar to those in the bone marrow mast cells.

A study of 20 G-banding metaphases of bone marrow showed a normal male karyotype, negative for t(9;22). Fluorescence in situ hybridization (FISH) for *BCR-ABL1* gene rearrangements (LSI BCR/ABL ES Probe; Abbott Molecular, Abbott Park, IL) performed on freshly harvested bone marrow aspirate smears was positive in 30% of cells. *BCR-ABL1* fusion signals were also observed in 89% of cells on touch imprints from the orbital mass. We also performed combined immunofluorescence for CD117 and FISH for *BCR-ABL1* on bone marrow core biopsy sections by using previously described methods¹ and demonstrated *BCR-ABL1* fusion signals in CD117+ cells (Figs 3A, 3B; arrows). Reverse transcription polymerase chain reaction (RT-PCR) for *BCR-ABL1* fusion transcripts coding for p190 as well as for p210 and p230 products was negative by both a multiplex real-time PCR protocol² and nested PCR protocol.³ Additional laboratory testing showed an elevated serum tryptase level of 12.8 ng/mL (normal,

Fig 1.

Fig 3.

< 10 ng/mL; > 20 ng/mL is required as minor criterion for systemic mastocytosis [SM]). No *KIT* D816V mutation was detected by allele-specific oligonucleotide PCR, and no *JAK2* V617F mutation was detected by pyrosequencing.⁴

Treatment and follow-up. Because of the presence of both the *BCR-ABL1* fusion gene and extramedullary disease in this patient, chronic myelogenous leukemia (CML) in blast phase was diagnosed. The patient was treated with oral tyrosine kinase inhibitor (TKI) dasatinib at 140 mg daily and low-dose Ara-C at 20 mg/m² for 10 days every 28 days. The patient had completed 11 courses of treatment at last follow-up (11 months after initial diagnosis). All of his bone lesions and orbital mass had resolved, and he had achieved complete bone marrow morphologic and cytogenetic remission. Repeated RT-PCR for *BCR-ABL1* was negative (as at initial diagnosis). The treatment had no major adverse effects.

Discussion

We describe an unusual case of CML presenting as various forms of mast cell neoplasms. The diagnosis of blastic phase of CML⁵ was established by the presence of extramedullary disease in bone and soft tissue, against a background of cells bearing the *BCR-ABL* fusion as determined by FISH analysis. Karyotyping and RT-PCR failed to detect the *BCR-ABL* translocation, probably because of cryptic and complex Philadelphia chromosome translocation.⁶ All lesions resolved with TKI dasatinib treatment, and the patient achieved complete remission.

One of the most challenging features of this case was the classification of the mast cell infiltrates. First, the femoral bone pathologic fracture showed abundant and confluent CD117+ and tryptase-positive mast cells, which suggested SM. However, the defining major criterion of SM of multiple compact clusters of mast cells was not met.

In fact, a diagnosis of SM is not recommended when there is a diffuse increase in mast cells in the marrow without fulfillment of the other criteria for SM.^{7,8} In our patient, the minor criteria for SM, such as an elevated tryptase level of more than 20 ng/mL and the presence of the D816V *KIT* receptor gene mutation, were not fulfilled.⁸ Thus, it is likely that the sheets of CD117+ and tryptase-positive cells in the left femoral lesion represented CML blasts with mast cell differentiation. The term myelomastocytic leukemia is used to encompass mast cell differentiation of underlying immature (> 5%) leukemic cells, and more than 10% of these cells have basophilic or metachromatic granules.⁹ Most cases of myelomastocytic leukemia are associated with acute myeloid leukemia with maturation and sometimes with myelodysplastic syndromes or myeloproliferative neoplasms.⁷ Of interest, in a review of the literature, we identified only two cases consistent with myelomastocytic leukemia associated with blastic phase CML, both without extramedullary disease.^{10,11}

The second presenting lesion of extramedullary orbital tumor was characterized by the presence of immature mast cells, which were CD34±, CD117+, and partially tryptase positive, associated with marked eosinophilia. This variation in cell differentiation with a common *BCR-ABL1* gene rearrangement supports the theory that the cell of origin in these mast cell proliferations arising in CML is a pluripotent hematopoietic cell.¹⁰

In addition, our patient had unique clinical manifestations, presenting as blastic phase CML without the typical blood-associated or usual marrow features of CML, except for FISH being positive for *BCR-ABL1* in the bone marrow cells. In addition, karyotype and RT-PCR for p190 as well as for p210 and p230 were negative. Extramedullary involvement occurs in 10% to 40% of patients with blastic phase CML, usually in well-established cases; however, rarely, it can be the presenting manifestation.^{12,13} Isolated lytic bone lesion as

extramedullary disease has been reported in CML rarely (2% of patients), usually as skeletal blastic phase, although half of patients may show only the chronic phase on bone biopsy.¹³⁻¹⁵

Our case illustrates the dramatic effect of dasatinib in achieving complete remission of the blastic phase of chronic myelogenous leukemia at multiple sites and in controlling myelomastocytic leukemia. Although imatinib is the first-line treatment for CML,^{12,16} the second-generation TKI dasatinib has been proven superior for blastic phase CML, and it has recently been suggested as first-line therapy for CML.¹⁷ Higher rates of return to chronic phase and complete cytogenetic and molecular remission have been achieved with dasatinib.¹⁸

In our patient, therapy with the TKI dasatinib resulted in complete response of orbital and bone lesions, suggesting that the variable cell-line involvement was a manifestation of single underlying CML, and made the presence of two different diseases unlikely, as previously reported. Two similar cases have been reported in the literature. Agis et al¹⁹ reported a case of SM associated with CML, both processes supported by characteristic molecular analysis. In their patient, therapy with imatinib resulted in remission of both diseases.²⁰ Cairoli et al¹⁹ reported a case of CML associated with *c-kit* gene mutation and transient marrow mastocytosis.¹⁹ In previously reported cases of myelomastocytic leukemia, prognosis has been poor, with survival length of usually less than 1 year.^{7,9}

In summary, this case represents an interesting stem-cell neoplasm biologically and clinically. The variation in cell differentiation with a confirmed *BCR-ABL1* fusion supports the theory that the cell of origin in CML is a pluripotent hematopoietic cell. Recognizing the unusual pathologic features, including this variant presentation of CML, allowed us to reach a correct diagnosis, which led to specific targeted therapy.

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