HOSPITAL CHRONICLES 2015, 10(1): 39–40

IMAGES IN MEDICINE

Systemic Mastocytosis

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KEY WORDS: *systemic mastocytosis; cladribine; chemotherapy; myeloproliferative disorder; dasatinib; interferon-alpha; mast cell leukemia*

A 64-year-old man was admitted to the Hematology ward in July 2012 due to neutropenia and thrombocytopenia. The only symptom in the month preceding his admission was significant weight loss. Based on clinical and laboratory investigations, specifically bone marrow aspiration and biopsy (Figure), the patient was diagnosed with aggressive systemic mastocytosis (WHO 2008 ICD-0 code 9741/3).

The patient initially received treatment with cladribine 8.5 mg once daily in 2-hour intravenous infusion for a 5-day period/28-day cycle. Following the completion of a 5-cycle treatment course with cladribine, thrombocytopenia improved, but there was no significant change in neutropenia, while the hematocrit remained stable. However, the patient did not show any clinical improvement. Thus, he was reevaluated with bone marrow biopsy, which showed 40% infiltration by malignant mast cells. There was underlying disease of myeloblastic/myeloproliferative neoplasm unclassifiable with 3%

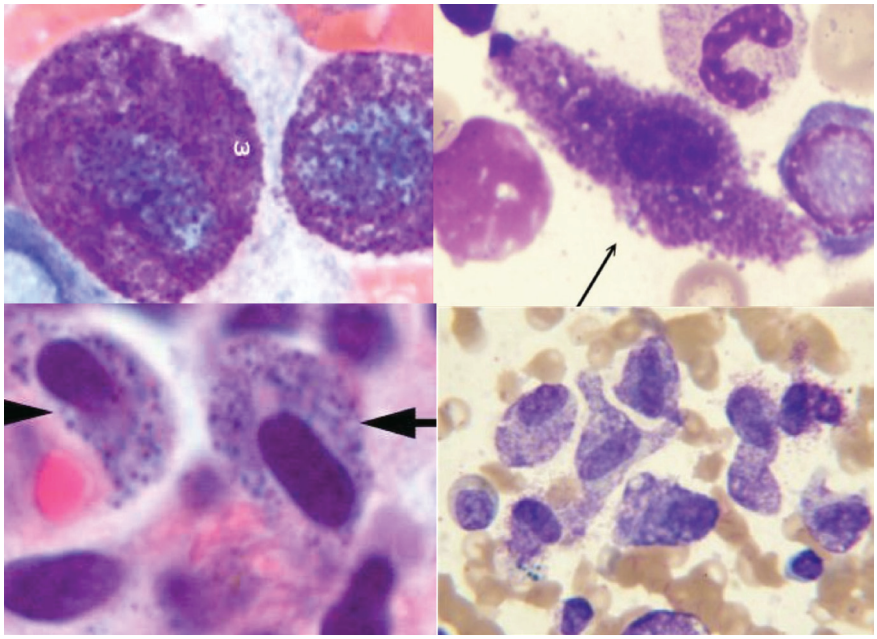

FIGURE. Mast cells (arrows) show abundant purple granules and oval to spindle nuclei in contrast to round and reniform normal nuclei.

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Manuscript received September 25, 2014; Revised manuscript received December 28, 2014; Accepted January 7, 2015

Conflict of Interest: none declared

CD34 positive myeloblasts (*systemic mastocytosis associated hematological non-mast cell disorder* - SM-AHNMD).

The patient was considered refractory to cladribine, therefore it was decided to administer standard acute myeloid leukemia chemotherapy induction with a 7-day course of cytarabine 100 mg/m^2 continuous infusion and idarubicin 12 mg/m^2 for 3 days followed by a second cycle with 5 days cytarabine infusion and 2 days idarubicin. The patient experienced prolonged aplasia after each chemotherapy cycle and his course was complicated by severe pneumonia which required hospitalization for several weeks. There was no hematologic improvement and the bone marrow biopsy showed persistent infiltration by malignant mast cells (30%) and presence of 2-3% myeloblasts (SM-AHNMD).

Because of the poor response to standard chemotherapy, the patient was offered investigational treatment with dasatinib. He received dasatinib 100 mg once daily for a 4-month period. The patient initially seemed to respond to the new therapy, albeit at the expense of significant side-effects. However, soon afterwards his clinical condition worsened and this treatment was discontinued. Treatment plan was subsequently changed to a trial of interferon-alpha (IFN-α). The starting dose of IFN-α was $3\times10^6\times3$/week and it was gradually increased to IFN-α $4.5\times10^6\times5$/week. The patient tolerated IFN-α relatively well, and this time he showed clinical improvement, having regained his appetite and putting on weight. However, the patient experienced treatment related hematologic toxicity, especially thrombocytopenia while he remained transfusion independent. Nevertheless, a hematologic improvement was confirmed on blood smear examination, pending reassessment with a new bone marrow biopsy.

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Systemic mastocytosis is a rare disease, characterized as a myeloproliferative neoplasm coming from clonal proliferation of abnormal mast cells in one or more extra-cutaneous organs.[1-8] Presence of multifocal clusters of morphologically abnormal mast cells in the bone marrow is considered as the major criterion.[2] Minor diagnostic criteria comprise elevated serum tryptase level, abnormal mast cell expression of CD25 and/or CD2, and presence of the KIT mutation D816V. At least one major and one minor or at least 3 minor criteria have to be fulfilled to establish the diagnosis of systemic mastocytosis.

Systemic mastocytosis is a progressive neoplastic disorder that has no known curative therapy, except perhaps for allogeneic hematopoietic stem-cell transplantation, which may turn out to be a viable therapeutic option.[9] It is classified as *indolent* mastocytosis, with no organ dysfunction and a good prognosis, mastocytosis associated with other hematologic disorders *(SM-AHNMD), aggressive* mastocytosis, characterized by impaired organ function, and *mast cell leukemia*, with >20% mast cells in the bone marrow, no skin lesions, multi-organ failure, and a poor prognosis.[2]

Several antineoplastic drugs and approaches have been employed for the treatment of patients with aggressive systemic mastocytosis and mast cell leukemia, some based on the inhibition of KIT D816V in neoplastic cells.[1-4,7,8] However, results remain unsatisfactory and treatment of advanced systemic mastocytosis remains one of the most challenging areas in clinical hematology. Even combined chemotherapy and hematopoietic stem cell transplantation may fail, which dictates the need to develop new drugs and treatment schemes and approaches for these patients.[9]

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