

Variants of systemic mastocytosis: A report of three cases

Sistemik mastositoz: Üç olgu sunumu

İbrahim Sarı¹, A. Yasir Bahar¹, Mustafa Pehlivan²

ABSTRACT

Advanced systemic mast cell neoplasms are very rare tumors and systemic mastocytosis is in the form of atypical leukemic infiltration of neoplastic mast cells to bone marrow and/or other organs. In this study, histological, immunohistochemical, flow cytometry, and molecular genetic findings of three patients that showing the increase in mast cells in the bone marrow discussed in terms of aggressive systemic mastocytosis, mast cell leukemia, systemic mastocytosis with associated clonal hematological non-mast lineage disease and myelomastocytic leukemia differential diagnosis in the light of the scientific literature. *J Clin Exp Invest* 2015; 6 (1): 65-68

Key words: Mast cell, neoplasm, differential diagnosis

ÖZET

İleri sistemik mast hücreli neoplaziler oldukça nadir tümörlerdir. Sistemik mastositoz, kemik iliği ve/veya diğer organlara neoplastik mast hücrelerinin atipik lösemik infiltrasyonu biçimindedir. Bu çalışmada kemik iliğinde mast hücre artışı gösteren 3 olgunun histolojik, immünohistokimyasal, flowsitometri ve genetik bulguları, ileri mast hücreli neoplazmlar -agresif sistemik mastositoz, mast hücreli lösemi, mast hücre dışı klonal hematolojik bir hastalıkla beraber olan sistemik mastositoz- ayırıcı tanısı açısından tartışılmıştır.

Anahtar kelimeler: Mast hücresi, neoplazi, ayırıcı tanı

INTRODUCTION

Systemic mastocytosis (SM) is defined as a myeloproliferative neoplasm, in the World Health Organization (WHO) 2008 classification. Mastocytosis consists of a spectrum of disorders related to the proliferation and accumulation of mast cells in one or more organs. The 2008 WHO classification of SM recognizes four major subtypes: Indolent SM, SM with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), aggressive SM (ASM), and mast cell leukemia (MCL). Additionally, the differential diagnosis of advanced systemic mast cell neoplasms also includes myelomastocytic leukemia (MML) [1].

CASE 1

A 77 year-old- male patient had anemia, leukopenia and multiple skin nodules. In routine complete

blood counts (CBC), hemoglobin 119 g/L, platelets 50x10⁹/L, white blood cell (WBC) is 3,3x10⁹/L were detected. Whole body scintigraphy was seen increased involvement in general skeletal system bone marrow (especially in axial bones). Serum tryptase activity was 175 ng/ml. On histopathological examination of the bone marrow biopsy were seen multifocal infiltration pattern. About 30% of bone marrow was infiltrated by, spindle-to-oval shaped, multifocal, compact cell clusters. These cells were positive for CD117 and mast cell tryptase by immunohistochemistry (Figure 1A-B-C). Flow cytometric analysis of neoplastic mast cells revealed the detection of CD13, CD33, HLADR, CD34, CD117, CD2 and CD25 antigens. Cytogenetic studies were positive for 47XY (trisomy 8). D816V KIT mutation and extra genetic material were detected with PCR. The case was diagnosed as ASM. Steroid therapy was made. The patient is still alive.

¹ Departments of Pathology, Faculty of Medicine, University of Gaziantep, Gaziantep, Turkey

² Departments of Internal Medicine, Hematology, Faculty of Medicine, University of Gaziantep, Gaziantep, Turkey

Correspondence: A. Yasir Bahar,

Departments of Pathology, Faculty of Medicine, University of Gaziantep, Gaziantep, Turkey Email: ayasirbahar@gmail.com

Received: 15.11.2014, Accepted: 22.12.2014

Copyright © JCEI / Journal of Clinical and Experimental Investigations 2015, All rights reserved

CASE 2

A 63 year-old- male was presented with signs of anemia and thrombocytopenia. Hemoglobin level was 120g/L. Over 20% of the increase in blast cells on peripheral blood smear was revealed. Blastic cells were increased more than 70% on histopathological examination of the bone marrow biopsy. These blasts were showing a diffuse interstitial pattern defined as loosely scattered cells without compact aggregates. These cells were positive for CD117 and mast cell tryptase by immunohistochemistry (Figure 2 A,B,C). Flow cytometric immunophenotyping showed that the blastic cells expressed CD13, CD33, MPO, HLADR, CD34 and CD117 but lacked CD2 and CD25. The case 2 was diagnosed as MML. The patient has died after the first course of 7+3 induction chemotherapy regimen period.

CASE 3

A 4 year-old- female child was presented with epigastric pain, bone pain and pallor on July, 20, 2011. On physical examination, distinct hepatomegaly and mild splenomegaly were detected. There was no evidence of hepatic dysfunction and hypersplenism. CBC revealed hemoglobin 62 g/L, platelets $17 \times 10^9/L$, WBC $19,2 \times 10^9/L$. Sedimentation rate was 72 mm/hour. The peripheral blood examination was filled with blasts. About 80% of bone marrow was infiltrated by blast cells in a diffuse interstitial pattern. Blastic cells were positive for CD117 and mast cell tryptase by immunohistochemical staining (Figure 3A,B,C) and flow cytometry was revealed CD33, 13, MPO, HLADR, CD34, CD117, CD2 expression. Cytogenetic studies showed t (8,21) and 18, 19, 20 chromosomal monosomy, respectively. The case 3 was also diagnosed as MML. The patient has achieved remission after chemotherapy (AML-BFM-2004 protocol) and bone marrow transplantation are preparing.

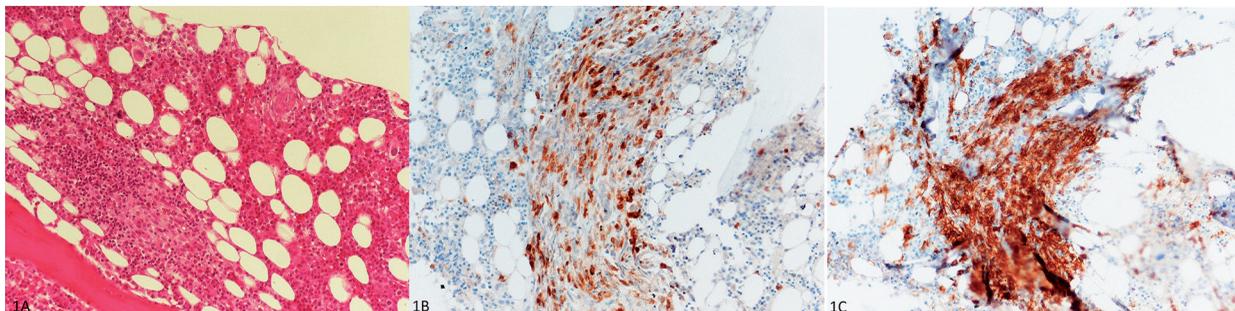


Figure 1. Case 1, Bone marrow biopsy; A: Hypercellular bone marrow with multifocal, dense, spindle to round shaped cells accumulation (HE, x 100), B: CD117 immunopositivity in blastic cells (x 200), C: Mast Cell Tryptase immunopositivity in blastic cells (x 200)

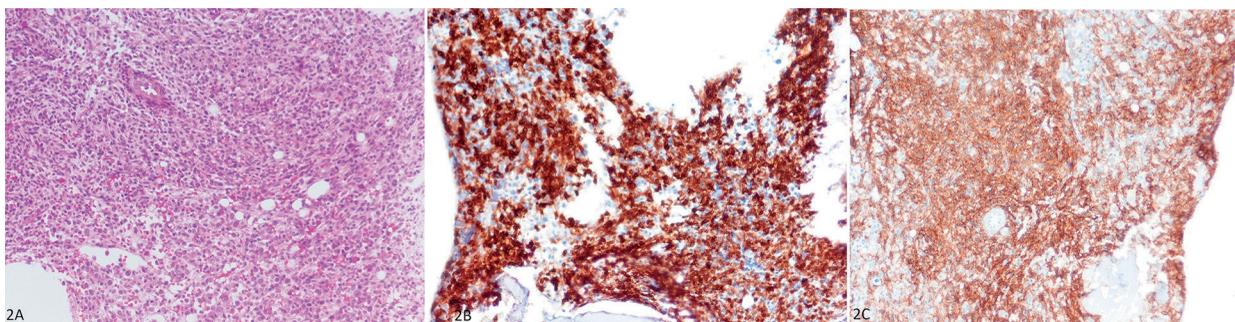


Figure 2. Case 2, Bone marrow biopsy; A: The blasts were showing a diffuse interstitial pattern (HE, x 200), B: CD117 immunopositivity in blastic cells (x 200), C: Mast Cell Tryptase immunopositivity in blastic cells (x 200)

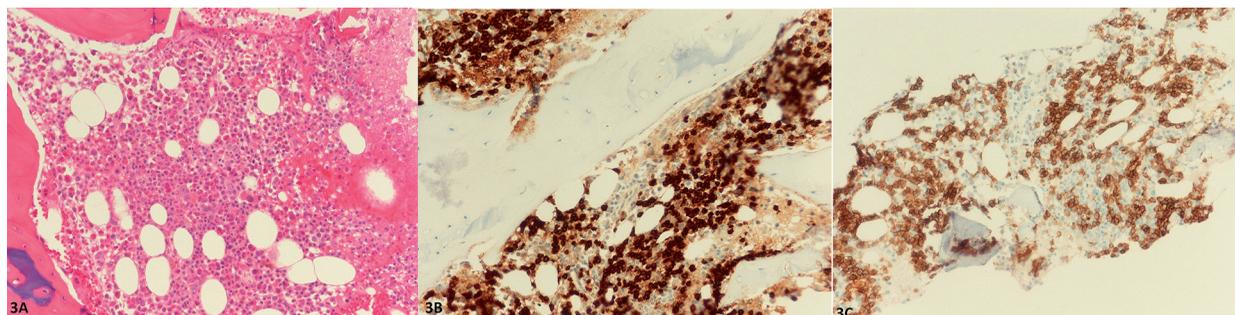


Figure 3. Case 3, Bone marrow biopsy; A: The blasts were showing a diffuse interstitial pattern (HE, x 200) B: CD117 immunopositivity in blastic cells (x 200), C: Mast Cell Tryptase immunopositivity in blastic cells (x 200)

DISCUSSION

Mastocytosis is defined as a clonal, neoplastic proliferation of mast cells with collection in one or multiple organ [2]. It is characterized by multifocal compact clusters or cohesive infiltrates of abnormal mast cells. Mastocytosis is divided into subtypes based on clinical findings and distribution of the disease [3].

Mastocytosis may occur at any age. Cutaneous mastocytosis is most commonly seen in childhood and may be at birth. Systemic mastocytosis is generally diagnosed after the second decade. About 80% of patients with mastocytosis have findings of skin involvement. In systemic mastocytosis the bone marrow is almost always involved [1].

In cutaneous mastocytosis (CM), mast cell infiltration is limited to the skin and typically seen together with articular symptoms in childhood. Clinical progress is benign and may regress spontaneously. The adult cutaneous disease has an indolent course [4].

The diagnosis of SM requires one major and one minor criterion or at least three minor criteria of classification of WHO 2008. While Indolent SM must have one or more “B” findings, 2 or more “B” findings are required for diagnosing SM. ASM and MCL are required one or more “C” findings [1].

Our first case provides at least one major and one minor criteria for SM diagnosis, according to the WHO 2008 classification. He has also “C” findings with the platelet counts $50 \times 10^9/L$. Therefore our case is compatible with the ASM. SM may also be associated with a SM-AHNMD, such as myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), acute leukemia, lymphoma, or plasma cell myeloma. In SM-AHNMD, full WHO diagnostic criteria for both SM and the AHNMD should

provide. AML develops as a second malignancy for about 20-30% of patients with SM. On histopathologic examination the mast cells and the cells representing AML are seen as separate areas [5,6].

MCL is a rare and aggressive type of SM [7]. It is characterized by the leukemic spread of mast cells. The bone marrow and other extracutaneous organs infiltrated by atypical mast cells, which composed of diffuse and/or multifocal dense areas. Neoplastic cells show the properties of SM. Additional clonal myeloid disease does not exist.

MML is a rare disease that has previously been described in patients with advanced myeloid neoplasms (most commonly refractory anemia with excess blasts, a subtype of MDS, or AML) with elevated numbers of immature atypical mast cells who do not meet full criteria for SM [1,4,8,9,10]. MML typically presents with an increase in myeloblasts (>5%) as well as >10% metachromatic blasts in the peripheral blood and/or bone marrow but without focal dense mast cell infiltrates, without mast cell expression of CD2 or CD25 and without evidence of the D816V KIT mutation by PCR (Table1).

In case 2, an interstitial increase of blast cells in bone marrow biopsy suggests MML or MCL. Neoplastic cells showed the characteristics of both myeloid cells and mast cells. In contrast specified in Table 1; CD2, CD25 and mutations in KIT D816V were negative. Therefore, our findings observed in favor of the MML.

Similar to case 2; in case 3, blast cells show interstitial pattern and the characteristics of both myeloid and mast cells. Flow cytometry positive for CD2 in favor of SM. However, absence of focal and/or diffuse dense areas in bone marrow and absence of CD25 and mutations in D816V works were against to SM. Therefore, the case was considered as an MML shows aberrant expression of CD2. In

the literature, there is a case MML showing the aberrant expression of CD25 but no CD2 [1]. We think this is the first presentation reported that expression of CD2 in MML.

In conclusion, three rarely seen patients were presented at which increase in mast cells in the

bone marrow was observed. Differential diagnosis is discussed according to a WHO 2008 classification scheme. We think that the new classification criteria would be needed with increasing number of cases that features not identified findings in the WHO 2008 classification.

Table 1. Histopathologic and laboratory criteria for advanced systemic mast cell neoplasms

	ASM	SM-AHNMD	MCL	MML
Peripheral blood MC	-	-	+/- ^a	+
Blasts	-	+/-	-	+
Bone marrow		AHNMD findings	>20% Immature or atypical MC ^c <5% blasts	>10% MC ^c >5% blasts
Aspirate smear ^b >25% MC of total MC immature/atypical in smears or >25% MC of total MC spindled/ atypical in biopsy	+	+	+	+
MC infiltrate in Biopsy	Focal dense Aggregates	Focal dense Aggregates	Dense, interstitial and/or diffuse	Interstitial
Molecular genetic findings D816V activating KIT mutation in blood, BM, or other extracutaneous organ	+	+	+	-
MC immunophenotyping Tryptase and CD117	+	+	+	+
CD25 and/or CD2	+	+	+	-
Serum markers, Serum tryptase (ng/mL)	>20	>20	Usually >100	Usually >100

ASM, aggressive systemic mastocytosis; SM-AHNMD, systemic mastocytosis with an associated clonal hematological nonmast cell lineage disease; MCL, mast cell leukemia; MML, myelomastocytic leukemia; MC, mast cell(s); BM, bone marrow.

^a Less than 10% circulating MC is classified as a leukemic MCL.

^b Percentages in aspirate smears refer to percentage of all nucleated cells.

^c MC may include metachromatic blasts.

REFERENCES

- Arredondo AR, Gotlib J, Shier L, et al. Myelomastocytic leukemia versus mast cell leukemia versus systemic mastocytosis associated with acute myeloid leukemia: a diagnostic challenge. *Am J Hematol* 2010;85:600-606.
- Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603-625.
- Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435-453.
- Valent P, Sperr WR, Schwartz LB, et al. Diagnosis and classification of mast cell proliferative disorders: delineation from immunologic diseases and non-mast cell hematopoietic neoplasms. *J Allergy Clin Immunol* 2004;114:3-11.
- Valent P, Akin C, Sperr WR, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. *Br J Haematol* 2003;122:695-717.
- Horny H.P, Sotlar K, Valent P, et al. Mastocytosis: state of the art. *Pathobiology* 2007;74:121-132.
- Sperr W.R, Horny H.P, Lechner K, et al. Clinical and biologic diversity of leukemias occurring in patients with mastocytosis. *Leuk Lymphoma* 2000;37:473-486.
- Noack F, Sotlar K, Notter M, et al. Aleukemic mast cell leukemia with abnormal immunophenotype and c-kit mutation D816V. *Leuk Lymphoma* 2004;45:2295-2302.
- Valent P, Somorapoompichit P, Sperr WR, et al. Myelomastocytic leukemia: myeloid neoplasm characterized by partial differentiation of mast cell-lineage cells. *Hematol J* 2002;3:90-94.
- Valent P, Sperr WR, Somorapoompichit P, et al. Myelomastocytic overlap syndromes: biology, criteria, and relationship to mastocytosis. *Leuk Res* 2001;25:595-602.