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LETTER TO THE EDITOR

Systemic mastocytosis with associated *BCRABL1*-negative atypical chronic myeloid leukemia

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Dear Editor,

An 81-year-old man, complaining fatigue and weight loss, was referred to our center due to leukocytosis and mild anemia with thrombocytopenia (WBC, 40100/mm^3, Hb, 10.1 g/dL, PLT, 103000/mm^3). Physical examination revealed mild splenomegaly. A peripheral blood smear showed immature granulocytes, dysplastic neutrophils with hypogranularity, and pseudo-Pelger–Huet anomaly (Fig. 1a). A bone marrow (BM) aspirate revealed hypercellularity for age, left shifted myeloid hyperplasia without increased blasts (Fig. 1b). Dysplastic megakaryocytes, including hypolobated forms and micromegakaryocytes, were present. In addition, diffuse spindle-shaped mast cell with an eccentric oval nucleus was detected (Fig. 1c, d). Bone marrow biopsy specimens confirmed cellularity > 95% with increased myelopoiesis, reduced erythropoiesis, and no fibrosis (Fig. 1e). Paratrabecular round to spindled CD117-positive mast cells were organized in nodular aggregates of 15 to 20 elements (Fig. 1f). Additional studies on the BM showed a normal karyotype (46, XY). Polymerase chain reaction for *BCR-ABL1* was negative, as well *JAK2V617F*, *CAL-R*, and *MPL*. Amplicon-based next-generation sequencing (NGS) targeting entire coding or hotspot regions of a 38-multigene panel associated with myeloid malignancies was performed on whole bone marrow DNA using a Ion Torrent platform (Thermo Fisher Scientific, Inc.). A *KIT* c.2447A > T p.D816V mutation at a variant allelic frequency (VAF) of 45% and a *U2AF1* c.101C > T p.S34F (VAF 47%), a spliceosome machinery gene, were identified. Basal tryptase value was 55.6 ng/mL (reference range < 11.4 ng/mL). Flow cytometry showed aberrant CD2–CD25 expression in 8.7% of MS. A diagnosis of systemic mastocytosis (SM) with an associated hematological neoplasm (SM-AHN) was made, according to the recent WHO 2016 classification. (1) To our best knowledge, this is the first described case of SM with associated *BCRABL1*-negative aCML.

SM is a myeloid neoplasm and only a rare percentage is associated with hematological neoplasm. The diagnosis of SM is established when a major plus one minor criterion or three minor SM criteria are present. Major criteria are the presence of a multifocal clustering of mast cells in one or more visceral organs; minor criteria are represented by an abnormal morphology of mast cells, an activating mutation of *KIT D816V*, and levels of serum tryptase > 20 ng /ml (the last does not represent a valid criterion if the patient has another non-mast cell hematologic malignancy). aCML is a rare *BCR-ABL1* negative disease with left-shifted granulocytosis and with an estimated frequency of 1 to 2 cases for every 100 CML cases. aCML is defined by peripheral blood leukocytosis due to increased numbers of neutrophils and their precursors comprising ≥ 10% of leukocytes, dysgranulopoiesis, basophils usually < 2% of leukocytes, monocytes < 10% of leukocytes, hypercellular BM with granulocytic proliferation with or without dysplasia in the erythroid and megakaryocytic lineages, < 20% blasts in the blood and BM, and not meeting WHO criteria for myeloproliferative neoplasms (MPNs). (1) The

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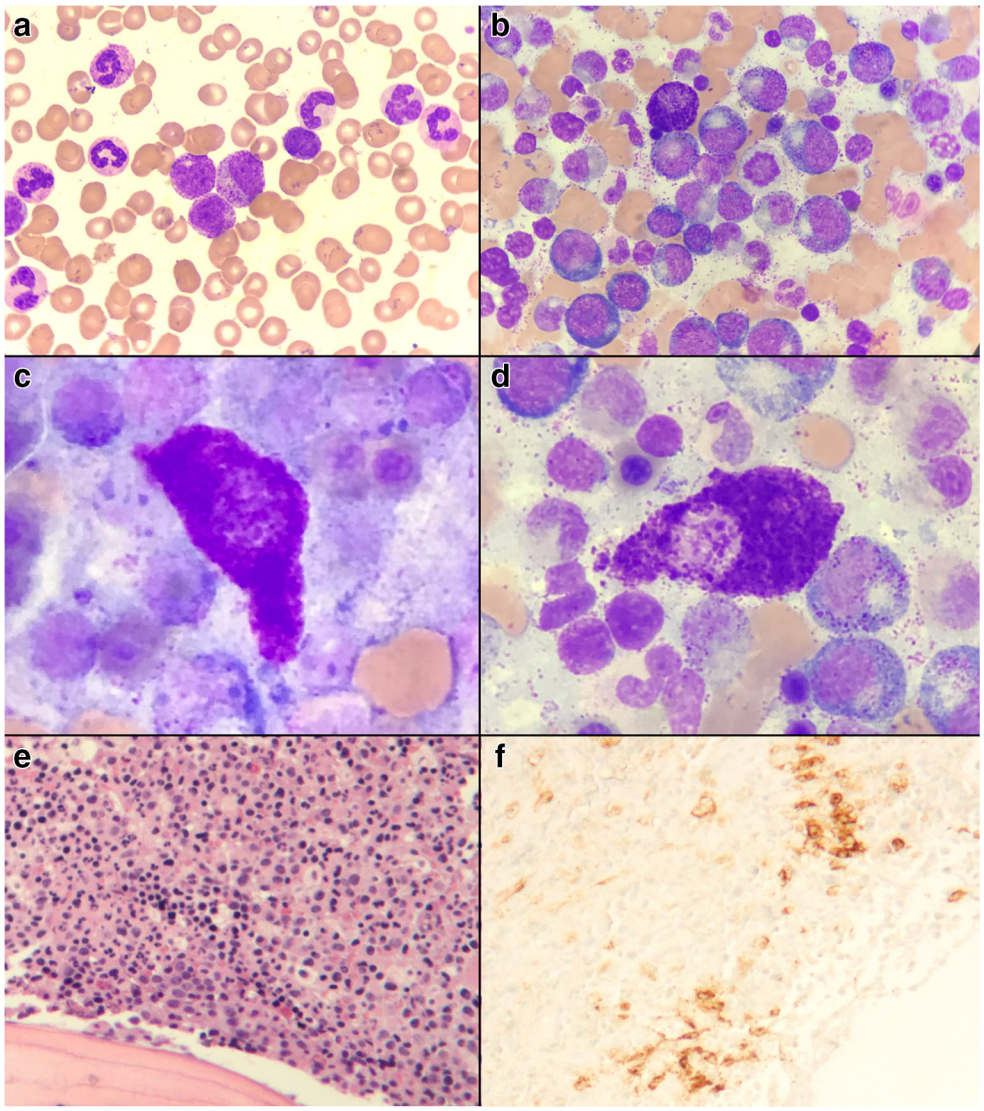

Fig. 1 (a) Morphology of peripheral blood smear showing immature granulocytes, dysplastic neutrophils with hypogranularity, and pseudo-Pelger–Huet anomaly (May–Grünwald Giemsa–MGG, ×100). (b) Bone marrow aspirate showing myeloid hyperplasia and full myeloid maturation; a mast cell is visible (MGG, 20×). (c, d) Cytologic abnormalities of mast cells: elongated cytoplasmic extensions (spindle-shaped mast cell) with an eccentric oval nucleus (MGG, ×500). (e) Hematoxylin and eosin stain of bone marrow trephine biopsy – 20X magnification: cellularity > 95% with increased myelopoiesis, reduced erythropoiesis, and no fibrosis. (f) Immunohistochemistry for CD117 – 40× magnification: nodular aggregates of mast cells

WHO classification has recently recognized a subgroup of SM-AHN, which is characterized by the presence of a concurrent neoplasm. Approximately 5% of SM cases are generally associated with myeloid tumors, such as myelodysplastic syndrome (MDS), MPNs, or acute myeloid leukemia (AML). Patients with aCML have an extremely poor prognosis with a median survival time of 14–29 months. The patient was initially started with low dose of hydroxyurea (500 mg/day). WBC count increased to 120000/mm^3, and he was treated with midostaurin half dose (50 mg twice daily in 4-week continuous cycles) (2). After 2 weeks the patient died from progression of leukemia.

Authors' contribution Conception and design: GC, MG
Patient management: VF, PC
NGS analysis: RA, GP, AP
Manuscript writing: GC, MG, GLN
Final approval of the manuscript: GC, MG, VF, RA, GP, AP, PC, GLN

Compliance with Ethical Standards

Conflict of interest Caocci G. declares that he has no conflict of interest; Greco M. declares that she has no conflict of interest; Frau V. declares that she has no conflict of interest; Casula P. declares that he has no conflict of interest; La Nasa G. declares that he has no conflict of interest;

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Statement of informed consent Informed consent was obtained from the patient included in the study

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