Acta Haematologica Polonica 51(1) • March 2020 • 51–55 • DOI: 10.2478/ahp-2020-0011

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CASE REPORT

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Systemic mastocytosis with chronic myelomonocytic leukemia followed by transformation into acute myeloid leukemia

Article history:
Received: 22.09.2019
Accepted: 22.12.2019

Marta Panz-Klapuch,
Krzysztof Woźniczka,
Anna Koclęga,
Anna Kopińska,
Kinga Boral,
Iwona Grygoruk-Wiśniowska,
Grzegorz Helbig*

Department of Hematology and Bone Marrow Transplantation, Medical School of Silesia, Silesian Medical University, Katowice, Poland

Abstract

Introduction: Systemic mastocytosis (SM) with an associated hematological neoplasm (SM-AHN) constitutes about 40% of all patients with SM. AHN commonly includes myeloid neoplasms and chronic myelomonocytic leukemia (CMML) is seen in about 30% of these patients. Case report: A 67-year-old male presented to hematologist with fatigue and significant weight loss. Abdominal ultrasound and computed tomography (CT) detected hepatosplenomegaly, abdominal lymphadenopathy, and ascites. He was anemic with leukocytosis and eosinophilia. Trephine biopsy showed > 30% of spindle-shaped mast cells. The *KITD816V* mutation was present. Serum tryptase level was elevated to 62 ng/mL. The patient was diagnosed with aggressive SM and received six cycles of cladribine with partial response. Three years later, he developed severe anemia. Eosinophilia and monocytosis (5.6 × 10^9/L) were demonstrated in blood film. Hepatosplenomegaly and abdominal lymphadenopathy were also present. Trephine biopsy did not demonstrate the presence of spindle-shaped mast cells, but dysplasia in erythroid and myeloid lineages was evident. The histological result of lymph node biopsy as well as blood and bone marrow findings were in line with CMML. He received hydroxyurea, but he transformed soon into fatal acute monocytic leukemia. Conclusions: The prognosis of SM-AHN depends on AHN component. Leukemic transformation of AHN component may occur in a proportion of patients.

Keywords:
advanced systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm, chronic myelomonocytic leukemia, cladribine, *KITD816V*

Introduction

Mastocytosis is a group of rare and heterogeneous disorders resulting from the clonal proliferation of abnormal mast cells in extracutaneous organs including bone marrow, lymph nodes, spleen, liver, and gastrointestinal tract. In the new 2016 WHO classification, mastocytosis was removed as one of the subtypes of myeloproliferative neoplasms (MPNs) and listed as a separate entity. Mastocytosis may affect people at any age, but cutaneous mastocytosis (CM) is usually diagnosed in children who present with typical skin features (urticaria pigmentosa). Systemic mastocytosis (SM) is commonly seen in adults, and indolent (ISM) or advanced (advSM) variants exist. ISM is characterized by low mast cell burden, no evidence of "C" findings, or an associated hematological neoplasm (AHN). Smoldering SM (SSM) meets the criteria of ISM, but it is defined by ≥2 "B" findings, absence of "C" findings, or an AHN. Both ISM and SSM have relatively good prognosis. Conversely, advSM has more aggressive course and reduced survival, and it requires cytoreductive treatment. Advanced SM includes three main subtypes, namely, aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Mast cell sarcoma (MCS), one more subtype of SM, occurs extremely rare with a localized growth of atypical mast cells especially in the larynx, colon, and bone. The prognosis differs between the variants with the poorest outcome demonstrated for MCL and MCS [1, 2, 3]. The prognosis for SM-AHN varies with the type of AHN [3].

The patients with SM may present the so-called "B" findings (benign = organ involvement without its dysfunction) or "C" findings (consider cytoreduction = organ damage due to an excessive infiltration by neoplastic mast cells). The presence of ≥1 "C" finding is an indication for treatment commencement [2]. Detailed characteristics of "B" and "C" findings are shown in table I.

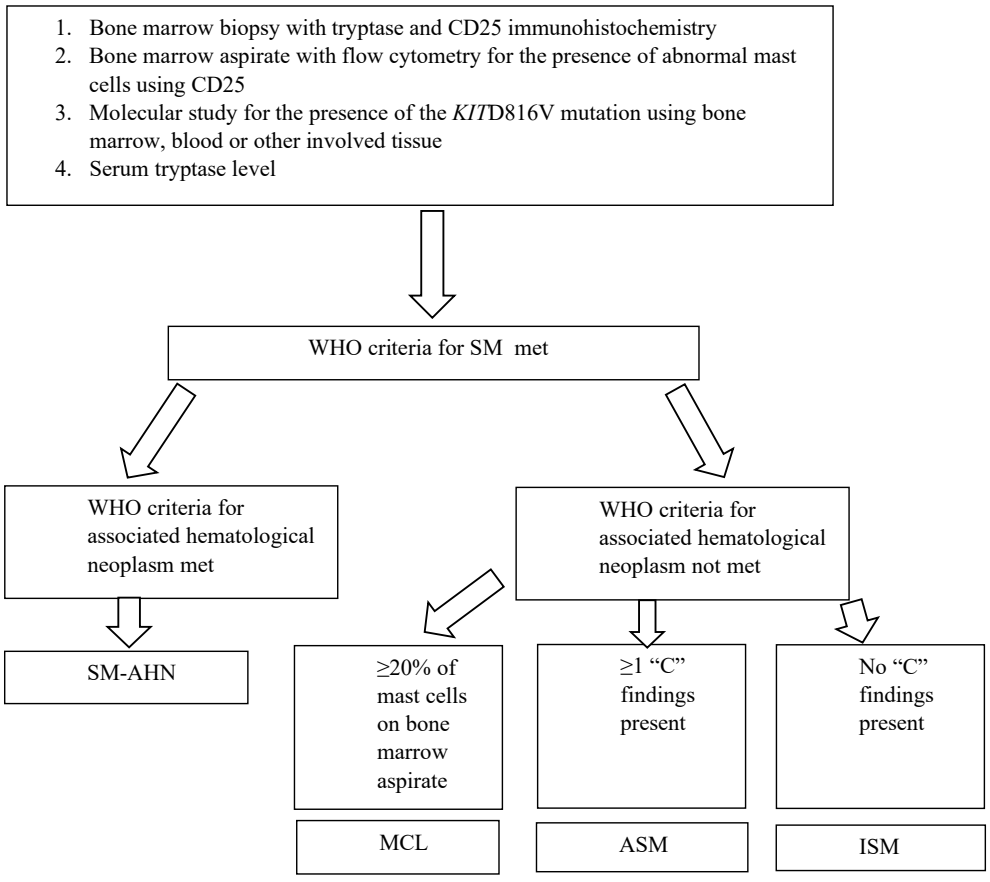
The diagnosis of SM requires 1 major plus 1 minor criterion or ≥3 minor criteria. The major SM criterion is the presence of mast cell infiltrates (>15 cells in aggregates) in bone marrow and/or other extracutaneous tissues. Minor SM criteria include: (1) >25% of abnormal mast cells in lesion tissue, (2) presence of *KITD*816V mutation, (3) the aberrant expression of CD25 with or without CD2 on neoplastic mast cells, and (4) serum tryptase levels >20 ng/mL [1]. The diagnostic algorithm for SM is presented in figure 1.

SM is usually diagnosed after the second decade of life. Male and female are equally affected. ISM accounts for 46% of all SM cases, whereas SM-AHN constitutes 40%, ASM 12%, and MCL 1–2%.

* Corresponding author: Grzegorz Helbig, Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Dabrowski 25, 40-032 Katowice, Poland; phone: +48 322591310, fax: +48 322554985, e-mail: ghelbig@o2.pl

Table I. "B" and "C" findings in SM [2]

"B" (benign) findings
1. Bone marrow biopsy with >30% infiltration by mast cells and serum tryptase level >200 ng/mL
2. The presence of features of dysplasia or myeloproliferation in non-mast cell lineage, but criteria for an associated hematological neoplasm not met; blood count normal or slightly abnormal
3. Hepatomegaly and/or splenomegaly with normal function and/or lymphadenopathy on physical examination or imaging
"C" (cytoreduction) findings
1. Bone marrow dysfunction due to mast cell infiltration with cytopenia in at least one line (absolute neutrophil count <1 × 10^9/L, hemoglobin level <10 g/dL, and platelet count <100 × 10^9/L)
2. Palpable hepatomegaly with liver dysfunction, ascites, and/or portal hypertension
3. Palpable splenomegaly with hypersplenism
4. The presence of large osteolytic lesions with or without pathological fractures
5. Malabsorption with weight loss as a consequence of gastrointestinal mast cell infiltration



AHHN – associated hematological neoplasm; ASM – aggressive systemic mastocytosis; ISM – indolent systemic mastocytosis; MCL – mast cell leukemia; SM – systemic mastocytosis; WHO – World Health Organization

Fig. 1. Diagnostic algorithm for SM [3]

Median survivals for above-mentioned variants are 198, 24, 40, and 2 months, respectively [4].

The clinical and molecular adverse prognostic variables in SM have been recently identified. The prognostic model was based on a study that included 580 patients with different SM variants. The combination of clinical and molecular variables confirmed the prognostic significance of the following: (1) mutations within the *ASXL1*, *RUNX1*, and *NRAS* genes, (2) advanced SM, (3) thrombocytopenia <100 × 10^9/L, (4) increased alkaline phosphatase, and (5) age >60 years [5].

SM-AHN meets the criteria of SM as well as the diagnostic criteria of AHN. Of note is that myeloid neoplasms account for majority of the reported cases (90%), whereas lymphoid tumors are rarely observed. AHN commonly includes myelodysplastic syndromes (MDS),

myeloproliferative neoplasms (MPN), chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML) [4, 6]. The rate of leukemic transformation is more frequent in SM-MDS when compared with SM-MPN or SM-CMML [7].

Herein, we report a patient with SM-CMML who achieved partial response (PR) after treatment with cladribine (2-CdA), but he subsequently progressed into fatal acute monocytic leukemia.

Case report

A 67-year-old male with medical history of chronic gastritis, arterial hypertension, and chronic coronary heart disease with severe anemia (Hgb <7 g/dL) and leukocytosis with eosinophilia was admitted in July 2014 to local hospital. He complained of easy fatigue and significant weight loss >20 kg within prior 2 months. He had lymphadenopathy (biopsy from supraclavicular lymph node was normal) and massive splenomegaly on physical examination. Trephine biopsy revealed >30% of spindle-shaped mast cells.

On admission to Hematology Unit in May 2015, he presented with hepatosplenomegaly, ascites, and peripheral lymphadenopathy. His skin was affected with macular rash located on the trunk and lower limbs. Abdominal ultrasound and computed tomography (CT) scan detected hepatosplenomegaly (liver 19 cm and spleen 20 cm), abdominal lymphadenopathy (>4 cm), and ascites. He was found anemic (Hgb = 9.2 g/dL) with an elevated leukocyte count (15 × 10^9/L) and normal platelet count. Blood film revealed eosinophilia (3.4 × 10^9/L) and single myelocytes and metamyelocytes. Monocytosis was not present. Bone marrow aspirate revealed eosinophils and single spindle-shaped mast cells (Fig. 2 and 3). The flow cytometry study of bone marrow aspirate did not demonstrate the presence of abnormal mast cell population. The *BCR-ABL*, *JAK2*V617F, *FIP1L1-PDGFRA*, and *PDGFRB* abnormalities were not detected, but the *KITD816V* mutation was present. Serum tryptase level was elevated to 62 ng/ml (normal <11.4 ng/mL). Karyotyping and fluorescence *in situ* hybridization (FISH) were normal. Biopsy of the skin revealed the presence of atypical mast cells. The patient was diagnosed with ASM and received six cycles of 2-CdA at 0.14 mg/kg/day for five consecutive days every 6 weeks. As a result, he achieved PR according to IWG-MRT/ECNM criteria [8]. The treatment with 2-CdA was well-tolerated with no grade 3 or 4 hematological and non-hematological adverse events. The standard prophylaxis with co-trimoxazole and acyclovir was used during the treatment and several months thereafter. Three years later, he became deeply anemic (Hgb = 4.7 g/dL). Eosinophilia (2.7 × 10^9/L) and monocytosis (5.6 × 10^9/L) were demonstrated on blood differential test. Hepatosplenomegaly and abdominal lymphadenopathy were also present. Macular rash was absent. Serum tryptase level was slightly elevated (15.1 ng/mL). Trephine biopsy and bone marrow aspirate did not demonstrate the presence of spindle-shaped mast cells, but monocytosis with dysplastic features in more than 10% of all cells in erythroid and myeloid lineages was detected. Eosinophilia in bone marrow was still demonstrated (Fig. 4). Flow cytometry did not detect increased proportion of blast cells, and the abnormal mast cells were also absent. Taken together, the patient fulfilled the criteria for CMML [9]. Liver biopsy was unremarkable, but histological examination of the excised abdominal lymph node was in line with CMML with eosinophilia. Karyotyping was normal and FISH did not reveal the presence of 5q31–33 abnormality. The patient received hydroxyurea, but he transformed soon into fatal acute monocytic leukemia. He expired in a local hospital and autopsy was not performed.

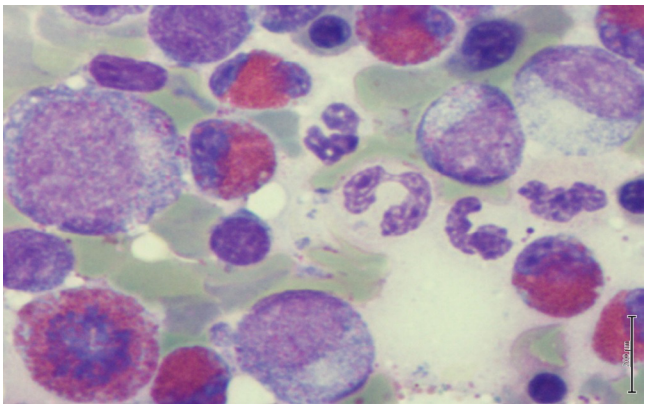


Fig.2. Predominance of eosinophils in the bone marrow [MGG stain 200×]

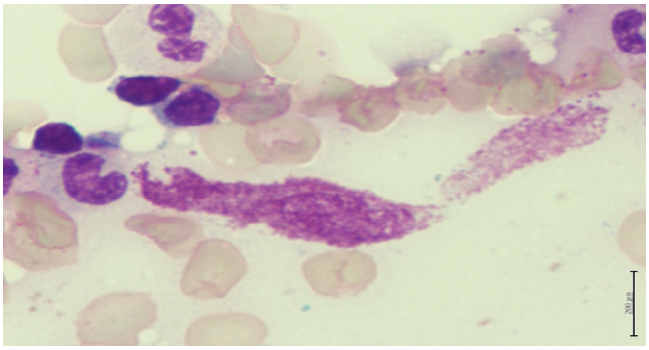


Fig. 3. Spindle-shaped mast cell [MGG stain 200×]

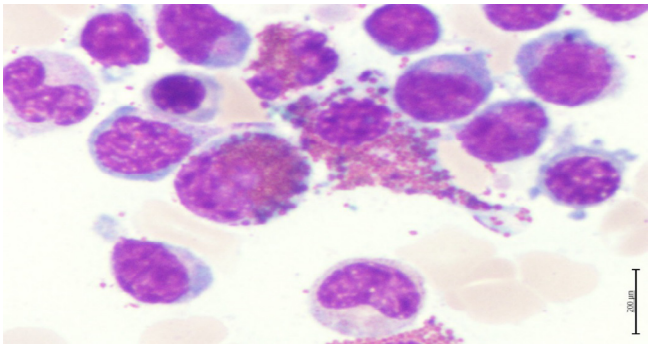


Fig. 4. Monocytes and eosinophils in the bone marrow [MGG stain 200×]

Discussion

SM with an associated hematological neoplasm is the second most common subtype of SM after ISM, and CMML remains the second most frequent associated myeloid neoplasm. It was demonstrated that CMML accounted for 29% of all studied patients among 138

reported by Mayo Group [7]. The other AHNs included MPN (45%), MDS (23%), and AML (3%). The lymphoid neoplasms were very rare and included lymphomas and myelomas. There was a single case of primary amyloidosis. The rate of leukemic transformation was the highest in SM-MDS (29%). The better life expectancy was noted for those with SM-MPN. The above findings were in line with those presented by other study groups [10, 11]. Of note is that 5-year survival for SM-AHN was 28% when compared with 61% demonstrated for other SM subtypes [10].

The diagnosis of SM component is usually incidental during the workup for hematological neoplasm. It should be mentioned that the *KIT*D816V mutation was found to be present in pluripotent hematopoietic stem cell. However, two clonal neoplasms may exist [12].

Most patients with SM-AHN were found to have an elevated serum tryptase level and detectable the *KIT*D816V mutation (>90%). The frequency of this mutation is dependent on the type of AHN, and the highest rate was observed in CMML. It was demonstrated less frequently in MPN and AML, and the mutation is not detected in lymphoproliferative disorders [13].

Karyotype abnormalities were detected in 32% patients with SM-AHN but rarely in patients with ASM [14, 15]. The abnormalities were most often found in patients with SM-AML [7].

Of note is that the diagnosis of SM-AHN is a challenge. As it was seen in our patient, the initial diagnosis of SM was determined based on the results of trephine biopsy that was performed to explain the cause of splenomegaly. The detection of mast cells in bone marrow prompted the further, more detailed diagnostic workup. It should be mentioned that mastocytosis is a rare part of the differential diagnosis and can be confirmed only after using the appropriate immunohistochemistry panel [11]. Interestingly, we did not observe the features typical for CMML during patient's first evaluation—monocytosis was not present in both the peripheral blood and bone marrow. Nevertheless, the enlarged abdominal lymph nodes were not taken for histopathological analysis at that time. It is not excluded that CMML was initially presented as an extramedullary manifestation and then progressed to leukemic form. Interestingly, eosinophilia was detected since first patient's presentation; however, the *FIP1L1–PDGFRA* and *PDGFRB* rearrangements were not found. It was demonstrated that the presence of eosinophilia in SM (except cases with the *FIP1L1–PDGFRA* gene fusion) has negative prognostic significance and may reduce event-free and overall survivals when compared with SM without eosinophilia [16]. The prominent eosinophilia is seen in about 34% of patients with SM-AHN, most commonly in patients with SM-MPN (56%). The latter includes chronic eosinophilic leukemia in 48% of patients. The clinical outcome of SM-MPN with and without eosinophilia is similar; however, those with the *FIP1L1–PDGFRA* transcript usually respond to imatinib mesylate [7].

The modern treatment of advanced SM should start with small molecule kinase inhibitor–midostaurin which has *in vitro* activity against kinase domain *KIT* mutation. Midostaurin (Rydapt) was approved by the U.S. Food and Drug Administration (FDA) for AdvSM in 2017; however, it is not reimbursed in Poland. Eighty-nine SM patients received midostaurin at a dose of 100 mg twice daily with the overall response rate (ORR) of 60% [17]. Several study groups presented their data on efficacy and safety of 2-CdA which remained a treatment of choice before midostaurin era. Ten patients with SM received 2-CdA and all patients responded to treatment; however, the response took several months and was incomplete and transient [18]. The largest series on 2-CdA in mastocytosis was presented by Barete et al. [19]. The study included 68 patients and the ORR was 50% for those with advanced disease (ASM 43% and SM-AHN 59%). Our patient responded to 2-CdA treatment and remained in PR for almost 3 years. The treatment was well-tolerated with no severe adverse events. Our small analysis of nine patients with advSM treated with 2-CdA has shown 60% ORR, but none of the patients achieved complete remission (unpublished data). The other therapeutic options for advSM include both standard and pegylated interferon-a. Imatinib mesylate is FDA-approved for the treatment of adult patients with ASM without the *KIT*D816V mutation or with unknown *KIT* mutational status. The only curative option remains allogeneic stem cell transplantation [20].

Transformation into acute leukemia is not a rare event in patients with SM-AHN. The rate of transformation is found to be 13% in a large study by Mayo Group; however, only 6% of patients progressed from CMML category. Almost 30% of SM-MDS patients had leukemic transformation [7]. The treatment for leukemic transformation is unsuccessful with significantly reduced survival as it was seen in our case. In total, two out of nine patients from our cohort progressed into acute leukemia (1 SM-MDS and 1 SM-CMML) (data not published).

Conclusions

Diagnosis of SM-AHN is difficult and may require cooperation with other specialists when the symptoms of mast cell activation occur. The prognosis depends on AHN component. 2-CdA still remains a mainstay of treatment in Poland as midostaurin is not reimbursed. Leukemic transformation of AHN component occurs in a proportion of patients and has negative impact on survival.

Authors' contributions

MPK, GH – contributed equally, wrote the manuscript, collected data, critical revision. KW, AK, KB, IGW – collected data, critical revision.

Conflict of interest

The authors have no competing interest.

Financial support

Not applicable.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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