Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Case report/ Kazuistyka

Indolent systemic mastocytosis associated with multiple myeloma: A rare coexistence

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ARTICLE INFO

Article history:
Received: 04.03.2017
Accepted: 30.08.2017
Available online: xxx

Keywords:
- Systemic mastocytosis
- Multiple myeloma
- Associated hematological neoplasms
- Treatment
- Prognosis

ABSTRACT

Systemic mastocytosis (SM) includes a wide spectrum of clonal disorders characterized by an abnormal growth and accumulation of mast cells. SM may be associated with other hematological neoplasms (SM-AHN) among them the myeloproliferative neoplasms and myelodysplastic syndromes are the most common. The coexistence of SM with lymphoid malignancies has rarely been reported so far. The occurrence of SM associated with multiple myeloma (MM) is extremely rare and its prognosis remains unclear. The treatment of SM-AHM requires an individual approach. We report a male patient diagnosed with indolent SM associated with MM. He did not require the therapy for his SM, but started the treatment against MM. He received the induction regiment consisting of bortezomib, thalidomide and dexamethasone (VTD). After six cycles of VTD he achieved a very good partial response, but refused autologous stem cell transplantation as response consolidation and eventually died of myeloma progression a couple months later. Herein we discuss the likely pathophysiologic mechanisms underlying those two separate entities.

Introduction

Mastocytosis represents a group of heterogeneous diseases characterized by clonal proliferation and accumulation of mast cells (MCs) in various organs. The 2016 revision of the World Health Organization (WHO) classification distinguishes three major categories of SM: cutaneous mastocytosis (CM), systemic mastocytosis (SM), and MC sarcoma. SM is divided into five subtypes: indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis, SM with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL) [1]. CM affects children and may be present as maculopapular rash. Other forms of CM include diffuse cutaneous mastocytosis (DCM) and mastocytoma of skin. SM is usually seen in adults and is defined by multifocal MC aggregates in the bone marrow or other extracutaneous organs. The true incidence of SM remains uncertain and is estimated to be approximately 1 case per 10 000/annually [2]. The presence of at least one of C-findings (cytopenia, lytic lesions, malabsorption, liver insufficiency and hypersplenism) is sufficient for treatment initiation.

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http://dx.doi.org/10.1016/j.achaem.2017.08.006

Please cite this article in press as: Chromik K, et al. Indolent systemic mastocytosis associated with multiple myeloma: A rare coexistence. Acta Haematol Pol. (2017), http://dx.doi.org/10.1016/j.achaem.2017.08.006

In up to 40% of cases, SM-AHN [3], resulting in a combination of symptoms characteristic for each separate disorder. Chronic myelomonocytic leukemia (CMML) is reported to be the most common myeloid neoplasm associated with SM [4]. Lymphoproliferative neoplasms are much less commonly involved. To date, there have been 10 reported cases of non-Hodgkin lymphomas, 3 of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, 1 of hairy cell leukemia (HCL), and 1 of Hodgkin lymphoma (HL). SM associated with multiple myeloma (MM) has been documented in only 8 patients so far [5]. Herein, we describe a patient with indolent SM associated with MM.

Case report

A 62-year-old male was admitted to Hematology Unit presenting weakness and fatigue, being febrile (37.9 °C) with moderate pallor. He also complained of right ankle joint pain. He was non-atopic and denied a history of anaphylaxis, syncope, angioedema or aspirin hypersensitivity. His past medical history was insignificant. His complete blood count revealed severe normocytic normochromic anemia (hemoglobin; Hb; 6.9 g/dL) with a white blood cell (WBC) count of 16 G/L. Peripheral blood smear revealed slight anisocytosis with predominance of eosinophils (23%). The proportion of other cells was within normal range. Biochemistry and coagulation tests were normal. Serum immunoglobulin test revealed an elevated IgG level of 37.8 g/L (range 7–16), with normal levels of IgM and IgA. Serum protein electrophoresis (SPE) detected a monoclonal protein at 2.4 g/dL defined as IgG lambda on immunofixation. Beta-2 microglobulin and C-reactive protein levels were increased at 3.06 mg/L and 26.7 mg/L, respectively. Serum albumin was decreased: 3.2 g/dL. Serum free lambda and kappa light chains ratio was 0.12 (range 0.26–1.65). Urine protein electrophoresis was negative. X-ray skeletal survey detected numerous lytic lesions in thoracic and lumbar spine as well as in pelvis. His spleen was slightly increased (13.4 cm on abdominal ultrasound).

Bone marrow aspirate showed 13% of plasma cells, some of them with immature appearance. Flow cytometry analysis revealed more than 1.6% of clonal plasma cells with CD38 and CD138 positivity. No other abnormalities have been detected (Fig. 1). Bone marrow trephine biopsy was carried out, but the results were pending.

Conventional cytogenetic study revealed normal karyotype, no abnormalities were found by fluorescence in situ hybridization. The diagnosis of MM was established at stage IIA (Durie/Salmon staging system) and ISS 2 (International Staging System).

The patient started the induction with bortezomib, thalidomide and dexamethasone (VTD) regimen. Meanwhile, the results of trephine biopsy were available. Marrow was found to be hypercellular with focal reticulin and collagen fibrosis (Masson+). Immunohistochemistry revealed atypical CD117+, tryptase+ cells in clusters comprising 20% of total bone marrow cellularity. Megakaryocytes were quantitatively normal, however, a subset of them was hypolobated. Plasma cells (CD38+, CD138+) constituted 3% of total BM cellularity. The patient continued his VTD cycles. The extended diagnostic panel toward SM was initiated and revealed an elevated serum tryptase levels (457 ng/L, range <11.4) and the presence of a point mutation (Asp816Val) in the c-kit receptor. Nonetheless, there was no indications to start treatment for SM as the patient did not manifest the C symptoms.

The patient achieved a very good partial response after six cycles of VTD. Following the fourth cycle, the laboratory work-up revealed leukocytosis (WBC 13.17 G/L), and peripheral blood smear still revealed an increased proportion of eosinophils (17%). The test for the FIP1L1-PDGFRalfa mutation was negative. He remained asymptomatic for cutaneous or systemic symptoms of SM. The repeated flow-cytometry analysis of bone marrow found 0.012% of cells with the following phenotype: CD38++, CD138+++, CD19−, CD56+, CD45−, CD27−. In addition, 0.205% cells CD117+, HLA-Dr+/, CD25+, CD2+ were detected (Fig. 2). The patient was proposed to perform autologous hematopoietic stem cell transplantation for his MM, but refused. A half year later, he abruptly progressed with his myeloma. He was admitted to our

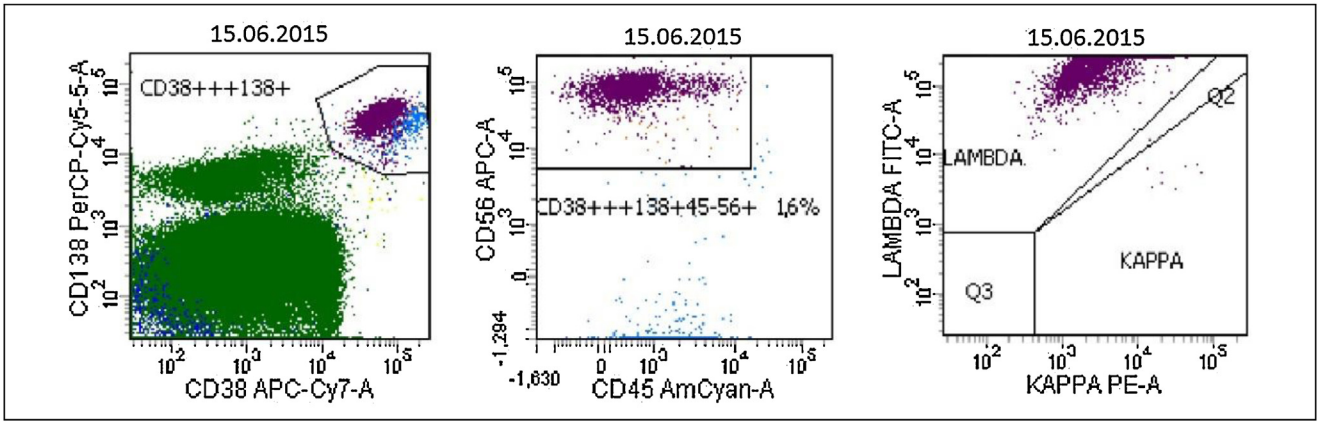

Fig. 1 – Flow cytometry study of bone marrow aspirate before anti-myeloma therapy (VTD)
Clonal plasma cells (1.6%) were present on flow cytometry analysis (purple gate). Plasma cells were positive for CD38, CD138, lambda and CD56. FITC indicates fluorescein isothiocyanate. Mast cells were not detected.

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