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Case report/ Kazuistyka

Indolent systemic mastocytosis associated with multiple myeloma: A rare coexistence

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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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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

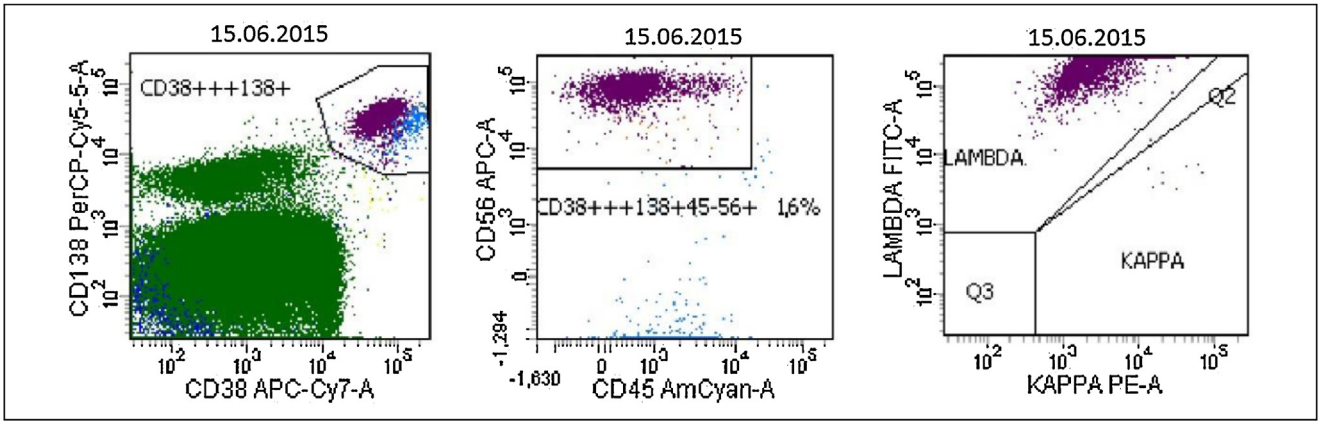

Fig. 1 – Flow cytometry study of bone marrow aspirate before anti-myeloma therapy (VTD)
Clonal plasma cells (1.6%) were present on flow cytometry analysis (purple gate). Plasma cells were positive for CD38, CD138, lambda and CD56. FITC indicates fluorescein isothiocyanate. Mast cells were not detected.

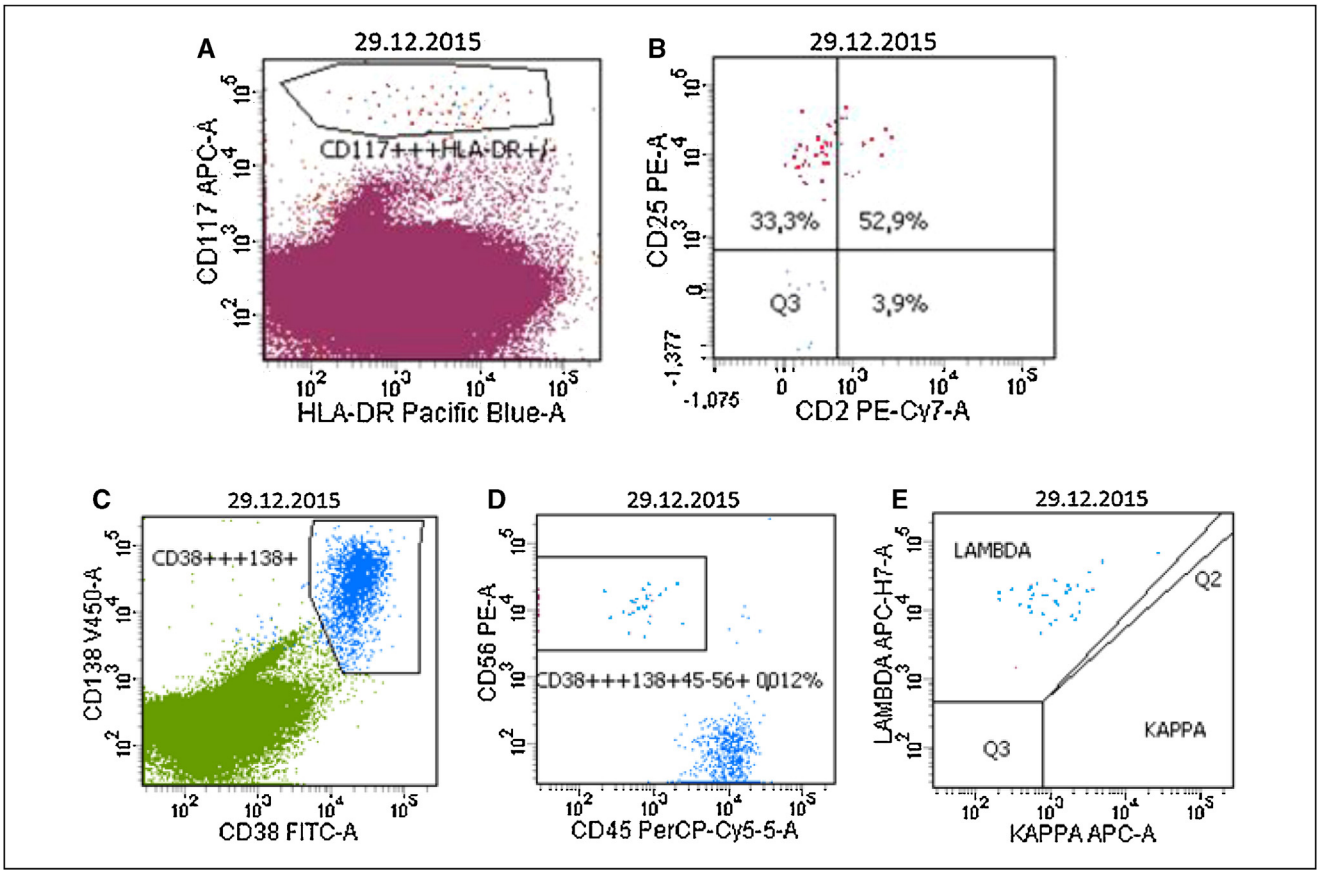

Fig. 2 – Flow cytometry study of bone marrow aspirate after anti-myeloma therapy (VTD)
The gating strategy used for the identification of the mast cells population (red events, 0.205%) within the CD117+ cells gated in A and CD25+, CD2+ gated in B. Flow cytometry analysis revealed also approximately 0.012% clonal plasma cells (blue gate) within CD38+++138+45-56+lambda+ gated in C, D, E.

institution after a 3-week history of fever of unknown origin, anorexia, weight loss and night sweats. Physical examination showed a moderate ascites. No lymphadenopathy or plasmacytomas were observed. Blood examination revealed anemia (Hb 7.9 g/dL), thrombocytopenia (98 G/L) and elevated WBC count (28.5 G/L). The patient showed liver dysfunction, elevated LDH and B2-microglobulin levels. SPE showed a monoclonal peak at 3.9 g/dL. Bone marrow aspirate and biopsy showed a 72% infiltration of atypical undifferentiated plasma cells with pleomorphism, prominent nucleoli and abundant blue cytoplasm. Abdominal ultrasound revealed significant ascites, lymphadenopathy and hepatosplenomegaly (liver 174 mm; spleen 151 mm × 75 mm). Paracentesis detected 93% of atypical plasma cells. He started with the PAD regimen (bortezomib, doxorubicin and dexamethasone). After one cycle of therapy his clinical condition dramatically declined and he passed away.

Discussion

A bone marrow biopsy with tryptase staining remains an initial procedure in multistep diagnosis of SM. Other tests such as MC immunophenotyping, cytogenetic/molecular studies, and serum tryptase levels may confirm the final diagnosis. While patients with ASM and MCL are symptomatic, those with ISM frequently present with skin lesions only and/or mediator-related symptoms. Most adult SM patients (80%) harbor the KIT D816V mutation, which has also therapeutic implications [5]. Diagnosis of SM may be established if one major plus one minor or three minor criteria are met (Tab. I).

The symptoms of SM are usually grouped into 4 categories:

- constitutional symptoms such as fatigue, weight loss, sweats and fever,
- skin symptoms,
- MC mediator-related symptoms,
- musculoskeletal symptoms, which include bone, muscle and joint pain.

In general, symptoms occurring in mastocytosis are mainly due to the release of chemicals from the MCs and thus producing symptoms associated with an allergic reaction. Flushing and gastric acid hypersecretion due to MC-associated histamine release are common. Heartburn, stomach aches, abdominal discomfort and diarrhea may occur. The liver, spleen and lymph nodes may become enlarged in some patients. Bones may also be affected by mastocytosis

Table I – WHO criteria for systemic mastocytosis

Major criterion	Minor criteria
1. Multifocal, dense aggregates of mast cells (15 or more) detected in sections of bone marrow and confirmed by tryptase immunohistochemistry or other special stains.	1. In biopsy section, more than 25% of the masts cells in the infiltrate have atypical morphology, or, of all the mast cells in the aspirate smear, more than 25% are immature or atypical. 2. Mast cells co-express CD117 with CD2 and/or CD25. 3. Detection of KIT point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs. 4. Serum total tryptase persistently >20 ng/ml (not a valid criteria in cases of SM-AHN).

Abbreviations: SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

and bone involvement manifests as lytic lesions. In aggressive SM, cytopenia, osteolysis, lymphadenopathy, hepatomegaly with impaired liver function, ascites or portal hypertension, and malabsorption, may also occur.

The difference between indolent and aggressive SM relies on the presence of C findings, which indicate organ dysfunction secondary to excessive MC infiltration. C findings include cytopenias, hepatic dysfunction, pathologic fractures, hypersplenism and gastrointestinal malabsorption [6].

SM-AHN is the second most common subtype of SM (after ISM), and is a distinct form of SM characterized by synchronous evolution of two separate clonal populations, one consisting of MCs and one as a second hematologic malignancy. Approximately 90% of SM-AHN represent a myeloid neoplasm such as myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), MDS/MPN (e.g., CMML), eosinophilic disorders, or acute myeloid leukemia (AML). Lymphoproliferative neoplasms are much less frequently found in this setting. Pardanani et al. reported on 7 patients (5.1%) with lymphoma, 5 patients (3.6%) with myeloma, and 2 patients (1.5%) with CLL in their study of 138 cases of SM-AHN [6].

The pathophysiologic relationship between SM with lymphoproliferative disorders remains unclear. In cases of SM associated with lymphoproliferative disorders, including plasma cell neoplasm, the D816V C-KIT mutation was detected in the neoplastic MCs but not in the lymphoid population, suggesting that SM and coexisting lymphoid neoplasm were clonally separate [7–10]. Interestingly, there are several lines of in vitro evidence demonstrating the ability of neoplastic MCs to support the growth of associated neoplastic lymphoplasmacytic population [11, 12].

The studies have shown the capacity of neoplastic MCs to induce the growth of lymphocytic neoplasms. Tournilhac et al. demonstrated that the human MC line HMC-1 stimulated proliferation of the malignant lymphoplasmacytic cells of patients with Waldenstrom's macroglobulinemia through interactions between CD154 on the MCs and CD40 on the lymphoplasmacytic cells [13]. In vitro studies also suggest a role of MCs in the growth of HL via their expression of CD30 ligand [14]. A similar relationship may exist between MCs and plasma cells as well. MCs secrete multiple cytokines including IL-6 and stem cell factor, both of which have been shown to induce plasma cell proliferation [15–17].

In summary, the co-existence of SM with MM does occur rarely. One should be aware of such co-occurrence. Each patient diagnosed with AHN requires an individual approach. The treatment should be directed against each separate entity and remains a great challenge. However, this was not a case in our patient. One may speculate on the potential pathogenic link between the presence of MCs and development and progression of MM, but it requires further studies.

Authors' contributions/ Wkład autorów

According to order.

Conflict of interest/ Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

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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