CASE REPORT

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Systemic mastocytosis associated with essential thrombocythemia

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Abstract

Mastocytosis comprises a spectrum of disorders characterized by abnormal growth of mast cells (MS). Four entities are recognizable according to WHO classification. Association of systemic mastocytosis (SM) with a chronic myeloproliferative neoplasia (SM-AHNMD) is the second frequently category. Published descriptions of the clinicopathologic features of SM-AHNMD are largely limited to individual case reports. We present the case of a 41-year-old woman with thrombocytosis and mild splenomegaly. Clinical suspicion was of chronic myeloproliferative neoplasia (CMN). Bone marrow trephine biopsy examination (histology and immunohistochemistry for CD117 and CD25) revealed a SM associated with CMN, essential thrombocythemia (ET) type. The JAK2 V617F (for CMN) was detected but KIT / Asp816Val (reported in ~80% of SM) was absent. We discussed the particularity of the cases correlated with a review of the literature.

Keywords: systemic mastocytosis, essential thrombocythemia, SM-AHNMD.

Introduction

Mastocytosis comprises a spectrum of disorders related to the abnormal growth and accumulation of mast cells in one or more organs. The 2008 World Health Organization (WHO) classification of systemic mastocytosis (SM) recognizes four major subtypes: (1) indolent SM, (2) SM with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), (3) aggressive SM, and (4) mast cell leukemia [1]. SM-AHNMD is an entity defined first time in the 2001 WHO classification of malignant tumors of the hematopoietic tissues and comprises all cases of SM with an associated non-mast cell lineage clonal hematological disease [2]. In the majority of patients with SM-AHNMD, a myeloid stem cell malignancy is diagnosed. These disorders include myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative disease (MDS/MPN), acute myeloid leukemia (AML), and chronic myeloproliferative neoplasia (CMN) [3, 4]. Because the limited clinical usefulness of the term "SM-AHNMD", some authors proposes its substitution by a prognostically more useful subcategorization that includes SM-MPN, SM-CMML, SM-MDS, and SM-AL [5]. We present a case of SM associated with a CMN, essential thrombocythemia (ET) type.

Patient, Methods and Results

In November 2008, we examined the first bone marrow trephine biopsy of a 31-year-old woman presenting with thrombocytosis (T – 820×10^9/L) and mild splenomegaly.

Morphological findings

The bone marrow trephine biopsy examination showed (Hematoxylin and Eosin stain sections) a normocellular bone marrow with a normal M/E ratio (4/1), without left deviation. The megakaryocytes were numerous, with large/giant form, with hypersegmentated nuclei. The megakaryocytes were disposed in perivascular loose clusters (Figures 1 and 2). Meticulous analysis of the whole biopsy specimen using high power magnification showed a few small perivascular foci consisting of spindle shaped cells (Figure 3), with loosely but uniformly scattered fine metachromatic granules (Giemsa stain sections), with intermingled macrophages and eosinophils, and a pronounced increase in reticulin fibers (Gömöri stain sections) (Figure 4).

Immunohistochemical findings

To confirm the histological suspicion of ET associated with SM, manual immunohistochemical

analysis for CD117/c-kit (DAKO, Denmark, dilution 1:400) and CD25 (Novocastra, UK, dilution 1:50) were carried out on paraffin-wax sections using EnVision Dual Link system-HRP detection system (DAKO, Denmark). Few small clusters of mast cells positive for CD117/c-kitt (Figure 5) and with abnormal expression of CD25 (Figure 6) were detected within the perivascular areas.

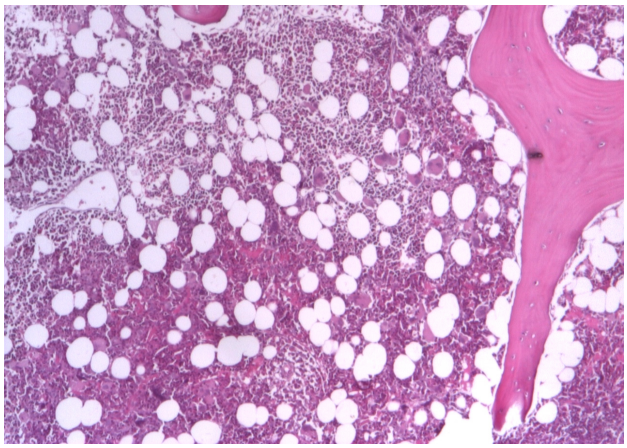

Figure 1 – ***Normocellular bone marrow, with increased number of megakaryocytes (HE stain, ob. 4×).***

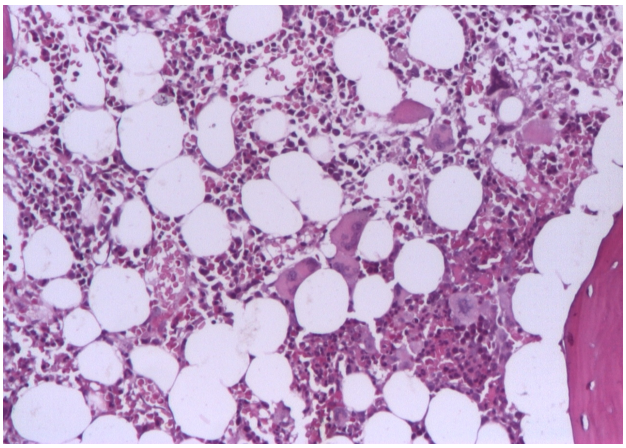

Figure 2 – ***Large/giant hyperlobulated megakaryocytes in small perivascular clusters (HE stain, ob. 10×).***

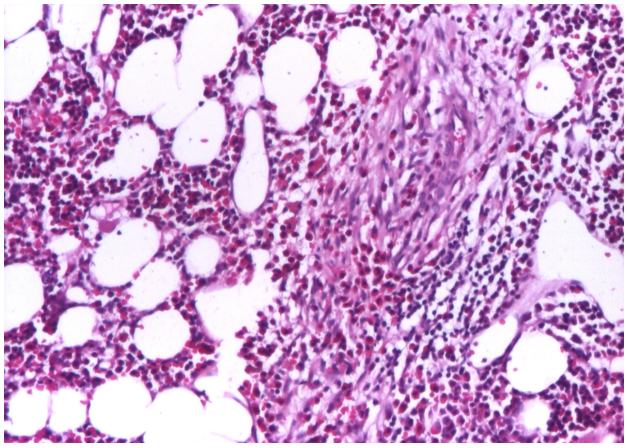

Figure 3 – ***Few small perivascular foci consisting of spindle shaped cells (HE stain, ob. 10×).***

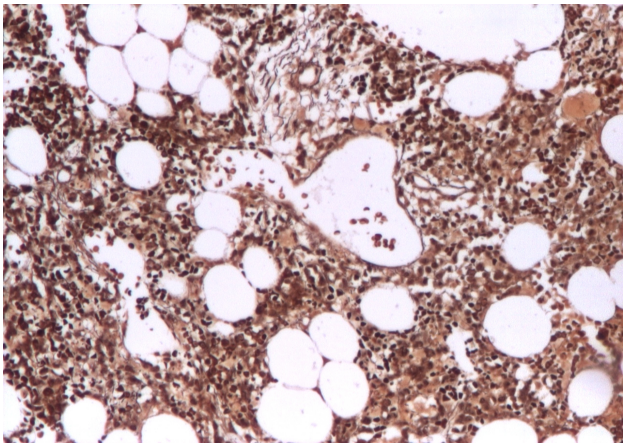

Figure 4 – ***Perivascular increase in reticulin fibers, corresponded with MC foci (Gömöri stain, ob. 10×).***

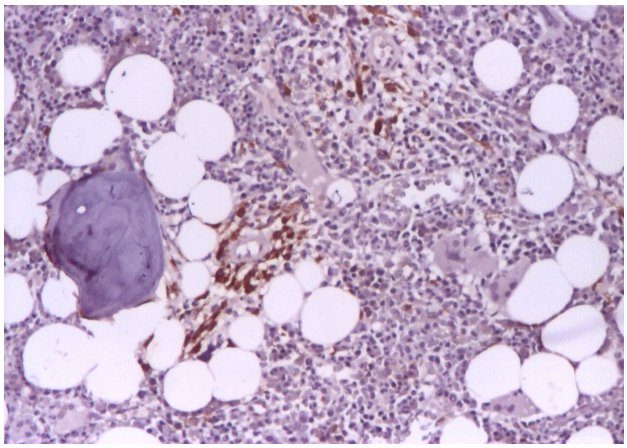

Figure 5 – ***The MC expresses CD117 (IHC stain for CD117, ob. 10×).***

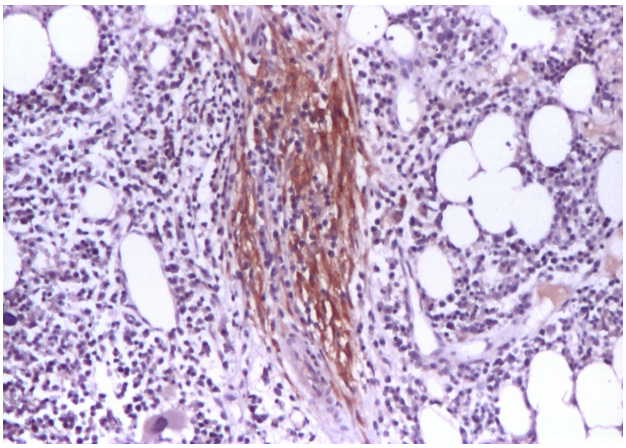

Figure 6 – ***Aberrant expression of CD25 in malignant MC (IHC stain for CD25, ob. 10×).***

Molecular findings

The molecular biology detected a somatic point mutation in the pseudokinase domain (V617F) of the JAK2 gene, but without detection of Asp816Val (D816V) somatic mutation in the catalytic domain of the KIT gene.

Treatment and follow-up

The patient was treated with interferon-α (IFNα). In the follow-up, two others bone marrow trephine biopsies were performed (January 2010 and January 2011) without significant improvement of the histological findings, but the thrombocytes are in the normal range.

Discussion

The mast cells (MCs) are multifunctional hematopoietic cells that develop from uncommitted CD34+ progenitors. MCs express a unique composition of antigens and can be distinguished from basophils and all other types of hematopoietic cells by their biochemical and functional properties [6–8]. MCs are involved in vascular cell regulation and allergic disease states [9]. Normal bone marrow MCs are round to oval, with densely packed, uniform cytoplasmic granules (Giemsa stain, Toluidine Blue stain) and a non-lobulated nucleus [10].

SM is characterized by a proliferation of mast cells and the formation of characteristic mast cell lesions [10]. MCs in SM vary in morphologic features from fairly typical mast cells to larger, fusiform cells with loosely but uniformly scattered fine granules [11, 12].

SM-AHNMD is a specific subtype of SM. In the group with associated hematologic disease, the AHNMD should be classified according to WHO criteria [1]. Some authors propose the tentative term "myelomastocytic leukemia" for such cases [13].

We presented a case of SM associated with JAK2-positive ET. The diagnosis of SM in our case is based on the presence of one major criterion (the presence of multifocal dense infiltrates of more than 15 mast cells in bone marrow biopsy), and one minor criterion (the expression of CD25 surface markers in c-kit positive MCs). The others three minor criteria (not presented in this case) include elevated serum α-tryptase levels >20 ng/mL (which may be monitored during the course of the disease), the presence of c-kit mutations in bone marrow and/or other tissue MC, and the presence of >25% abnormal spindle-shaped mast cells in bone marrow and/or tissues [14, 15].

Immunohistochemistry on routinely processed bone marrow biopsy specimens demonstrated that CD25 is expressed exclusively on mast cells of those cases with morphologically and molecular biologically confirmed mastocytosis, but not on mast cells in states of mast cell hyperplasia, enabling an abnormal or neoplastic phenotype of mast cells to be defined [16, 17].

In the published studies, SM-AHNMD is the second most common subtype of SM (after indolent SM) [4, 17], with a frequency of SM-AHNMD between 21% [18] and 44% [12]. The myeloid malignancies most commonly associated with SM in the literature are MDS, AML, and CMML [3, 4, 19]. According to all published data, the most frequent (39%) myelogenous neoplasm associated with SM is CMML, which is included in the group of MDS/MPS [17, 20, 21]. The published cases of SM-AML cover the whole spectrum of subtypes according to the FAB (French-American-British) classification, with a peak for AML types M2 and M5 [3, 20]. Most subtypes of chronic myeloproliferative disorders have been described as AHNMDs, including essential thrombocythemia, polycythemia vera, and other unclassifiable myeloproliferative disorders [3, 22, 23]. The SM-AHNMD concept would fit for the rare occurrence (about 10%) of SM associated with lymphoproliferative disorders/plasma cell dyscrasias. Interestingly, monoclonal gammopathy of unclear significance is much more common in patients with mastocytosis than overt B-cell neoplasms/plasma cell myelomas and, moreover, point mutations of C-KIT have been detected in circulating B-cells [5, 17].

Clinical symptoms associated with SM result from mast cell-derived chemical mediators. Symptoms include flushing, tachycardia, pruritis, abdominal cramping, peptic ulcer disease, and diarrhea. Infiltration of various organs by the malignant cells may cause cytopenias, osteoporosis, pathologic fractures, hepatosplenomegaly, lymphadenopathy, and malabsorption (these are called "c-symptoms"). The c-symptoms are indicative criteria for aggressive forms of mastocytosis [24]. In the presented case, a SM was not clinical suspected; the clinical picture resembled that of a MPN. The clinical records of the patients with SM-AHNMD never included a differential diagnosis of mastocytosis [17]. Symptoms and signs due to skin or other organ infiltration or mediator release are unusual in cases associated with *de novo* AML, probably due to the short clinical course. These findings have been more typically described in cases associated with CMML [25, 26]. However, in some MDS patients the symptoms may also be caused by mediator production by clonal cells. Valent P *et al.* reported a massive leukemic spread of MC in patients with MDS [27].

A pathogenetic hallmark of the majority of SM cases in adults is the Asp816Val (D816V) somatic mutation in the catalytic domain of the KIT gene [28, 29]. The proto-oncogene KIT encodes c-kit protein, a transmembrane receptor tyrosine kinase expressed on hematopoietic stem cells, mast cells, melanocytes, and germ cells. Stem cell factor–c-kit interaction promotes the growth and differentiation of mast cells from CD34+ bone marrow or peripheral blood stem cells [30]. These mutations result in ligand-independent auto phosphorylation of the receptor and have been detected in the human mast cell leukemia cell line HMC-1 as well as in systemic mast cell disease. MC-1 carries two c-kit point mutations: Val560Gly in exon 11 located in the juxtamembrane domain and Asp816Val in exon 17 in the phosphotransferase domain [31]. The former has been termed a "regulatory" type mutation and the latter an "enzymatic site" type mutation [32]. This transforming mutation results in enhanced mast cell survival and proliferation because of constitutive activation of the tyrosine kinase activity of KIT, independent of KIT ligand [31]. Asp816Val is the most common c-kit mutation described in patients with systemic mast cell disease including SM-AHNMD [22, 28].

The absence of Asp816Val c-kit mutation in our case is conforming to others authors observations [17, 19]. In systemic mastocytosis, presence of KIT D816V

is expected but not essential for diagnosis [33]. C-KIT mutations can be detected in about 80% of all patients with SM, especially when more sensitive molecular methods such as peptide nucleic acid mediated PCR clamping or nested PCR on pooled microdissected single mast cells are performed on routinely processed bone marrow biopsies [26, 34].

The exact pathogenesis of mast cell disease associated with myeloid malignancy remains unclear. The most likely answer is that both hematological diseases evolve from an early-uncommitted hematopoietic progenitor cell as a primary monoclonal disease, with further evolution into phenotypically different sub–clones [20, 35]. However, there is the possibility of the coincidental development of two distinct clonal hematological tumors [36]. The mast cell proliferation most likely represents the occurrence of an activating c-kit mutation in addition to at least one another genetic event in the myeloid stem cell [19]. Occurrence of a c-kit mutation in this progenitor cell would be expected to confer a proliferative advantage to the mutated clone as well as result in mast cell differentiation and proliferation. Additional genetic events may then occur resulting in the myeloid malignancy [37]. Alternatively, a subclone of the transformed stem cell may acquire the c-kit mutation resulting in coexisting mast cell disease [19]. The pathogenesis of mast cell disease associated with lymphoproliferative disease is unclear and c-kit mutations have not been reported in these cases [19].

The management of patients with SM involves attempting to control symptoms related to mediator release from mast cells and to curtail organ damage caused by infiltrating mast cells [38]. There is no effective treatment for SM. Treatment is directed at palliation of symptoms and inhibition of growth of the malignant cells. The choice of therapy is influenced by the patient symptoms and category of disease. Antihistamines, anticholinergics, mast cell stabilizers, and corticosteroids are useful for amelioration of symptoms in indolent SM due to chemical mediator release [15, 39, 40]. For patients with SM associated with c-symptoms, interferon-alpha (IFN) can be considered (induces usually partial responses in up to two-thirds of patients) [41]. The D816V KIT mutation of SM has been shown to be resistant to the tyrosine kinase inhibitor imatinib mesylate (Gleevec) both *in vitro* and *in vivo* [32]. These findings suggest that bone marrow mast cells and leukemic blasts may somehow be protected from this class of drugs by factors related to the bone marrow microenvironment [42]. PKC412 (N-benzoyl-staurosporine), an ST571 alternative inhibitor of multiple type III receptor tyrosine kinases, including the KIT tyrosine kinase, produce effect on peripheral blood mast cells, but, there was minimal reduction of the burden of mast cells within the bone marrow [43]. When SM is associated with a clonal non-mast cell hematologic malignancy, standard treatment measures are generally employed for the non-mast cell disease [44]. In general, evidence suggests that chemotherapy induces relatively short remissions, with a greater effect on the non-mast cell malignancy and little or no effect on the SM [45]. It must be stated that as far as we know at this time, the "SM" in SM-AHNMD should be treated like pure SM and the 'AHNMD' should usually be treated in the same manner as pure AHNMD. However, the resistance of neoplastic mast cells to cytoreductive drugs has to be borne in mind [17, 46].

Conclusions

To summarize, SM-AHNMD is a primarily morphological diagnosis based on a thorough investigation of bone marrow trephine specimens including CD117 and CD25 immunohistochemistry. Published descriptions of the clinicopathologic features of SM-AHNMD are largely limited to individual case reports. In most patients with SM-AHNMD, the diagnosis of mast cell disease is made concurrently with that of the myeloid malignancy.

Although the term systemic is often applied, the bone marrow is often the only documented site of involvement. Co-existing SM can easily be missed unless looked for during routine examinations of bone marrow aspirates, and biopsy sections, especially if the mast cell proliferation is not florid. The detection of SM-AHNMD may have important therapeutic implications. In SM associated with clonal hematologic non-mast cell-lineage disease, it is important to offer treatments that consider both diseases. The hematopathologist plays a crucial role in diagnosing or excluding mastocytosis in a given tissue specimen.

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