CASE REPORT

Systemic mastocytosis with acute myelomonocytic leukemia: a case report

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Abstract Bone marrow mastocytosis may be associated with many clonal non mast cell hematological neoplasms and its association with acute myeloid leukemia especially with t (8; 21) has been described. We describe an interesting case of coexistence of systemic mastocytosis with acute myelomonocytic leukemia in a young child. Diagnosis of acute myelomonocytic leukemia was based on bone marrow aspirate findings coupled with cytochemistry. Systemic mastocytosis was diagnosed on the basis of bone marrow biopsy findings showing blasts as well as multifocal dense mast cell infiltrates with spindling and atypical morphology which was confirmed on toluidine blue staining.

Keywords Acute myeloid leukemia · Toluidine blue · Systemic mastocytosis

Introduction

Systemic mastocytosis (SM) is a neoplasm of multilineage, myelomastocytic or mast cell committed hemopoietic progenitor cells. It is characterized by the involvement of at least one extracutaneous organ with or without skin infiltration and in most cases the aggregates of neoplastic cells are readily apparent on tissue sections but their mast cell lineage must be confirmed by the use of special stains [1]. Bone marrow mastocytosis may be associated with many clonal nonmast cell hematological neoplasms including myelodysplastic syndromes, myeloproliferative disorders, and acute myeloid leukemia [2]. Mastocytosis in association with acute myeloid leukemia especially with t (8;21) has been described in earlier studies [2–6] and there is evidence of origin of the mast cells from the leukemic clone [4, 6, 7].

Concurrent occurrence of SM may define a subset of patients with de novo AML and other myeloid neoplasms who have an adverse prognosis [2]. Mast cells in a bone marrow aspirate or biopsy may be either overlooked or missed especially when coexisting with another hematological disorder. Herein, we describe one such interesting case where the initial diagnosis of acute myeloid leukemia with mast cell hyperplasia was revised to systemic mastocytosis with acute myelomonocytic leukemia on the basis of bone marrow biopsy findings.

Case report

A 13-year-old girl, a daily wager, presented to us with high grade fever, pallor, generalized weakness and fatigability for 1 month and swelling of right lower leg

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associated with pain while walking for 15 days. On examination, she had pallor and hepatosplenomegaly of 2 cm and 3 cm respectively below the costal margin. During subsequent visits, she had additional complaints of bleeding from mouth and nose, vomiting and vertigo of recent onset. The hemogram showed hemoglobin 6.1 g/dl, total leukocyte count $13.6 \times 10^9/\mu\text{l}$ and platelet count $3 \times 10^9/\mu\text{l}$. Peripheral smear examination showed presence of 38% blasts with Auer rods and pelgeroid change in neutrophils. A clinical diagnosis of acute leukemia and deep vein thrombosis (DVT) of right leg was made and bone marrow examination was advised. The bone marrow aspirate smears were richly cellular and showed blasts with Auer rods along with maturing myeloid and monocytic cells. Many darkly stained mast cells were seen in the midst of the marrow particles (Fig. 1a) and were also prominent in the loose cellular trails (Fig. 1b). Cytochemical staining showed positive staining for Myeloperoxidase (MPO), sudan black blue (SBB) and non-specific esterase (NSE) in the blasts. Toluidine blue (TB) showed marked prominence of mast cells and highlighted their metachromatic granules (Fig. 3a). With this a diagnosis of acute myelomonocytic leukemia with mast cell hyperplasia was made. Haematoxylin and Eosin (H&E) stained section of the bone marrow biopsy showed 100% marrow cellularity and near total replacement of normal hemopoietic elements by sheets of blasts. In between, there were pale islands composed of aggregates of oval to spindle shaped cells with reniform to indented nuclei, moderate to abundant amount of clear, sparsely granular cytoplasm. These aggregates were found in paratrabeular (Fig. 2a) and perivascular location (Fig. 2b). Chloroacetate esterase

(CAE) staining showed these cells to be positive along with the maturing myeloid component amongst the sheets of blasts. These aggregates showed a mild condensation of coarse reticulin fibres and TB staining confirmed these aggregates to be of mast cells. In addition, many sprinkled mast cells were identified within the sheets of blasts (Fig. 3b) which were not very apparent on the H&E staining. The patient could not afford cytogenetics or molecular tests. In view of the bone marrow biopsy findings showing aggregates of mast cells with atypical morphology and spindling, a final diagnosis of systemic mastocytosis with acute myelomonocytic leukemia was made. The patient was put on supportive care with packed red cell and platelet transfusions and prophylactic antimicrobial therapy and has not yet been able to afford chemotherapy.

Discussion

Mastocytosis is a rare disorder and in a previous study done retrospectively on bone marrow biopsies, its incidence was found to be 0.3% of diagnosis established on those biopsies [8]. According to WHO, the diagnosis of mastocytosis can be established if one major and one minor criteria are present or if 3 minor criteria are fulfilled. The major criteria for systemic mastocytosis is the presence of multifocal, dense infiltrates of mast cells (15 or more mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs and confirmed by tryptase immunochemistry or other special stains. The minor criteria include: (1) In

Fig. 1 Bone marrow aspirate showing many darkly stained mast cells (a) in the midst of the marrow particles (Jenner & Giemsa $\times 400$) and (b) also prominent in the loose cellular trails (Jenner & Giemsa $\times 1000$)

Fig. 2 Aggregates of oval to spindle shaped mast cells with reniform nuclei, and clear, sparsely granular cytoplasm (a) in paratrabeular and (b) perivascular location (Hematoxylin & Eosin $\times 400$)

Fig. 3 Toluidine blue (TB) staining highlighting the metachromatic granules of mast cells (a) in bone marrow aspirate and (b) in biopsy showing aggregates and interstitial sprinkling (Toluidine blue $\times 400$)

sections more than 25% of the infiltrate are spindle-shaped or have an atypical morphology or more than 25% of the infiltrate are immature or atypical mast cells, (2) detection of KIT point mutation at codon 816 in bone marrow, blood or other extracutaneous organs, (3) co expression of CD 117 with CD2 and / or CD25 by mast cells and (4) serum total tryptase persistently above 20 ng/ml (unless there is an associated clonal myeloid disorder, where this parameter is not valid) [1]. This case fulfilled the major and first minor criteria for SM. As there was an associated AML, the initial diagnosis of AML with mast cell hyperplasia was revised to SM with associated clonal hematological non-mast cell lineage disease (SM-AHNMD). There are only few reported cases from India describing the association of mast cell disease with acute myeloid leukemia [7, 9].

Neoplastic mast cells have activating c-kit mutations which is a receptor tyrosine kinase required for their development, proliferation, and survival. Apart from the commonly described c-kit enzymatic site mutation Asp816Val detected in neoplastic mast cell disease, another mutation described is Asp816His mutation [2, 10]. Some studies show evidence of clonal origin of the mast cells from the same neoplastic clone as the blasts by demonstration of the same fusion transcript such as t (8; 21) in the tryptase positive mast cells and tryptase negative blasts by fluorescence in situ hybridization (FISH) [4, 6] and also by the demonstration of tryptase positivity by immunocytochemistry in some blasts (mast cell blasts) and mature mast cells [7]. In these studies, myeloablative stem cell transplantation resulted in either disappearance of the neoplastic mast cells [4] or

inconsequential persistence with gradual decline over time [6]. In our case, it was difficult to prove the clonality of mast cells and leukemic blasts due to non availability of immunocytochemistry, FISH and molecular studies.

The World Health Organization (WHO) classification system for myeloid malignancies in its upcoming revision, due out in 2008, considers mast cell disease as a myeloproliferative neoplasm and systemic mastocytosis as a subcategory of mast cell disease with bone marrow involvement [11]. At the same time, the WHO document distinguishes the usually KIT-mutated systemic mastocytosis from myeloid neoplasms associated with bone marrow mastocytosis and PDGFR mutations (e.g. FIP1L1-PDGFR α , PRKG2-PDGFR β) [12, 13] The latter are often associated with eosinophilia or basophilia and sensitive to treatment with imatinib.

A high index of suspicion is required to pick up mast cells in bone marrow smears especially in highly cellular marrow of acute leukemia where the mast cells sticking to the particles may be misconstrued as stain deposits. In such cases, the marrow should then be scanned in well spread areas where morphology is better preserved. The pale islands of mast cell aggregates as seen in the biopsy in this case may also be easily overlooked as histiocytes or fibroblasts. Metachromatic stains like TB and mast cell tryptase if available may be used to confirm the nature of these aggregates in such cases.

The clinical relevance of coexistence of mastocytosis with AML is not very well characterized. According to a previous study, concurrent occurrence of SM may define a subset of patients with de novo AML and other myeloid malignancies who have an adverse prognosis [2]. In patients with SM-AHNMD, separate treatment plans for the SM-component and the AHNMD should be established [14]. As clinically effective tyrosine kinase inhibitors that inhibit enzymatic-type c-kit mutations are being developed [15], detection of mast cell proliferation associated with myeloid malignancy may have important therapeutic implications.

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