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Acute Myeloid Leukemia with Marrow Mastocytosis: Does It Affect Prognosis?

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Abstract

Introduction: Mastocytosis can be associated with a hematological neoplasm of non mast cell lineage which is most commonly myeloid neoplasm. Diagnosis is difficult as the mast cell infiltrate can be subtle and masked by the associated malignancy. In this article, the cases of AML associated with marrow mastocytosis have been evaluated.

Material and Methods: The bone marrow at the time of initial presentation and post induction at follow up were evaluated in all the cases.

Results: Of the 9 cases, the peripheral smear and bone marrow aspirate showed variable percentage of blasts. The aspirate smears showed prominence of mast cells in all the cases. Following therapy though the percentage of blasts reduced, the mast cells still persisted. Partial remission was noted in 4 cases and 2 cases relapsed even after attaining complete remission at 28th day of post induction. Cytogenetic studies showed t (8:21) translocation in 2 cases.

Conclusion: Careful evaluation of bone marrow to look for coexisting mastocytosis at the time of initial diagnosis and post induction therapy is important to identify patients at risk as these patients are prone to frequent relapse or incomplete remission following therapy. Mastocytosis associated AML with t (8:21) translocation is extremely rare and carries a poor prognosis.

Keywords: Mastocytosis; Acute myeloid leukemia; Relapse

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Introduction

Mastocytosis is characterized by a clonal proliferation of mast cells that accumulates in one or more organs [1]. The bone marrow, liver, spleen, lymph nodes, or gastrointestinal tract with or without skin lesions are involved in Systemic Mastocytosis (SM). It can be associated with a hematological neoplasm of non mast cell lineage in 5% to 40% cases which is commonly myeloid and less frequently a lymphoproliferative disorder [2]. Diagnosis in the bone marrow is challenging as the mast cell infiltrate can be subtle and the morphology of the cells may be masked by the associated malignancy. In this article, we have analyzed cases of Acute Myeloid Leukemia (AML) associated with marrow mastocytosis and attempted to highlight the importance of recognizing this rare entity, in view of treatment stratification and significant prognostic implication.

Material and Methods

Patients diagnosed as acute myeloid leukemia with marrow mastocytosis were evaluated retrospectively in between January 2005 to August 2017. The demographic and clinical details were obtained from the medical records. The Giemsa stained peripheral smear and bone marrow aspiration cytology smears as well as biopsy were reviewed in all the cases. Following therapy, post induction marrows were also examined. Cases which were already diagnosed as AML outside and were on induction therapy, bone marrow was done after therapy to look for the remission status. A total number of 500 nucleated cells were counted and the number of blasts and mast cells were noted in all the cases. The bone marrow cellularity, degree of fibrosis, and presence or absence of morphologic dysplasia were also assessed. Cytochemical stains using Sudan Black B (SBB) and Periodic Acid Schiff (PAS) were done in all the cases. Toluidine blue staining was done to highlight the metachromatic granules of the mast cells. Immunophenotyping and cytogenetics were done in some cases. Immunohistochemistry (IHC) was done using CD34, MPO and CD117 antibodies on trephine sections. IHC was done using polymer Horse Radish Peroxidase (HRP) technique on fully

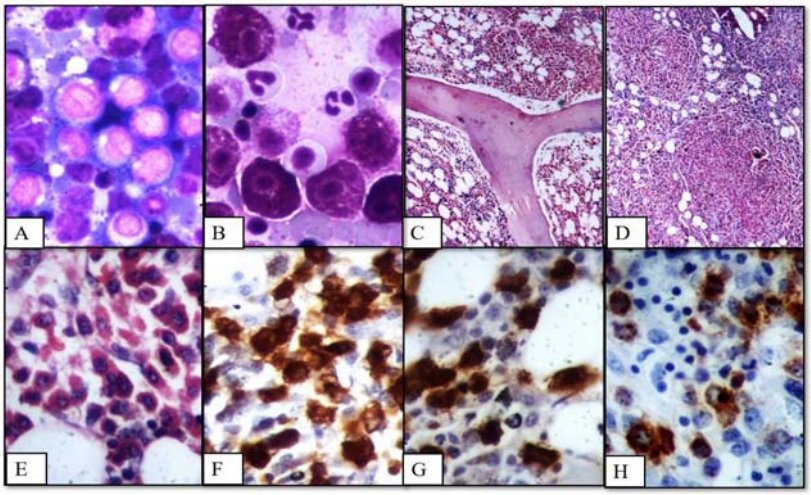

Figure 1: A. Aspirate particulate with prominence of blasts and mast cells (Giemsa × 100); **B.** Blasts that are 2 to 3 times the size of small lymphocyte with fine granules and round nuclei and few are indented (Giemsa × 400); **C.** Adequate trephine biopsy with nodules (arrows) of spindle shaped mast cells and blasts (H&E × 40); **D.** Spindle shaped mast cells with prominent nucleoli (H&E × 100); **E.** Prominence of mast cells (H&E × 400); **F and G**. IHC with MPO and CD34 positive in the blasts; **H**: IHC with CD117 shows intense positivity in nodules of mast cells.

Table 1: Clinicopathological features of cases of AML associated with mastocytosis at initial presentation.

Serial number	Age (years)/ Gender	Clinical presentation	Percentage of blasts on peripheral smears	Percentage of blasts on aspirate	Flow cytometry/ Cytogenetics	Bone marrow at 28th day post induction and follow up	Follow up
1	28/M	Fever, weakness, shortness of breath, petechiae, anaemia and splenomegaly	90	71	Flow cytometry **Positive Markers** CD 45 CD 117 CD 34 HLA – DR Cy MP0 **Negative Markers** CD 3 CD 4 CD 8 CD 33 CD 15 CD 14 CD 13 CD 7 Cy 79a CyCD3	Partial Remission with 7% blasts	
2	21/M	Fever, weakness, anaemia	40	45	Cytogenetics - t (8:21) detected	Complete remission	Relapse after 1 year
3	54/F	Fever, weakness	68	80		Partial remission with 14% blastsl	
4	55/F	Fever, malaise, shortness of breath	89	76	Cytogenetics - t (8:21) positive	Complete remission	Relapse after 1 year 3 months

automated immunostainer (X-matrix Elite; Biogenex).

Results

During the study period, a total number of 9 cases of AMLs with mastocytosis were identified. Of these, 4 were males and 5 females. The age of the patients ranged from 7 years to 65 years with a mean age of 35 years. Of these 9 patients, four of them presented initially with fever, weakness, malaise, shortness of breath and bleeding gums. One patient had petechial rashes and splenomegaly. The remaining 5 patients were diagnosed elsewhere as AML and were on induction chemotherapy. Peripheral smear and bone marrow aspirate showed variable percentage of blasts in all the 4 patients at diagnosis. The patients were diagnosed as AML based on morphology and cytochemistry. The blasts were positive for Sudan Black B and negative for PAS stain. Immunophenotyping was done in one patient. The blasts were positive for CD34, HLA-DR, MPO, and CD117 and negative for CD3, CD4, CD8, CD7, CD15, CD33 and CD 79a. Cytogenetic studies detected t (8:21) in another 2 patients. There was no evidence of any dyspoiesis in the erythroid precursors, granulocytes and megakaryocytic series. There was prominence of mast cells in all the cases. Cells had central round to oval nuclei with abundant cytoplasmic densely packed granules. The metachromatic granules were highlighted on toluidine blue staining. The mast cells were admixed with eosinophils and plasma cells in three cases. Bone marrow biopsy showed interstitial clustering of mast cells and blasts with increase in reticulin fibers. Nodules of spindle cells were seen in 1 case. IHC with CD34 and MPO highlighted the blasts and CD117 was expressed in both the blasts as well as mast cells (Figure 1). After completion of induction chemotherapy bone marrow aspiration was done again at 28th day post induction. Two patients showed

complete remission with blast percentage less than 5% and the other two patients had partial remission with presence of 7% and 14% blasts in the bone marrow aspirate. Though the percentage of blasts reduced significantly, the mast cells still persisted in all the patients ranging from 30% to 50%. On follow up, two patients with complete remission had relapse after a period of 1 year. Bone marrow at the time of relapse also showed mast cells admixed with the blasts. The clinicopathological features are listed in Table 1.

There were 5 patients who were diagnosed outside as AML and were referred to our institute for treatment. Bone marrow aspiration was done post-induction chemotherapy to look for remission status. The peripheral smear did not reveal any blast prominence. Aspirate showed persistence of blasts without any sign of remission of disease in 2 patients and partial remission in another 2 patients with blasts accounting for 8% and 16%. One patient showed hypo cellular marrow with complete remission. There was prominence of mast cells in all the cases ranging from 25% to 60%, forming clusters around the marrow particles.

Discussion

Systemic mastocytosis is sub-divided into five categories of which systemic mastocytosis with associated haematological neoplasm. SM-AHN is a distinct variant associated with hematological malignancy [3]. It is commonly seen after the second decade of life with a male preponderance and is rare in pediatric population [2]. The youngest patient was a 7 year old boy in this study. The patients present with symptoms related to systemic mastocytosis and the associated hematologic malignancy. Constitutional symptoms are commonly seen in these patients while skin lesions are infrequent [2]. Symptoms related to mast cell mediator-release are rare.

The most commonly associated myeloid neoplasms include chronic myelomonocytic leukemia and AML [4]. The other non–mast cell lineage disorders include Myelodysplastic Syndrome (MDS), Myeloproliferative Neoplasm (MPN), Acute Myeloid Leukemia (AML), chronic myeloid leukemia, MDS/MPN and unclassifiable MPN [5]. Lymphoid neoplasm like non Hodgkin lymphoma or plasma cell neoplasms are uncommon. Though the association of all FAB subtypes of AML has been documented in literature, M2 and M5 are the most common subtypes of AML associated with SM. In this study, all the cases were AML-M2 [6]. The associated hematological neoplasm may be diagnosed either concurrently, before or after the diagnosis of mastocytosis. Bone marrow is the most commonly involved extra cutaneous site and at times it is the only documented site of involvement. So a meticulous examination of bone marrow aspiration and biopsy is essential in all cases [5]. The coexistence of mast cells may be overlooked in routine bone marrow examination. Their presence is often masked as they tend to localize within the stromal fragments of the aspirate smears or obscured by overt blast population. On biopsy sections these mast cells may be missed if tiny aggregates are seen in the interstitium and they are also difficult to identify on routine stains. Hence ancillary techniques, like toluidine blue staining or IHC/Immunophenotyping often facilitates identification of these cells. In cases of post induction bone marrow evaluation, it has been seen that though the blast percentage drops down following therapy, the mast cells still persists. The mast cells are apparently better visualized at this stage following therapy-induced reduction in cellularity or repopulation of the marrow by normal hematopoietic elements.

In SM multifocal or diffuse infiltrates of mast cells with spindled morphology are seen in paratrabecular, perivascular, or interstitial locations. The other atypical morphologic features include immature chromatin, nuclear lobation or multinucleation. Associated reticulin fibrosis, osteosclerotic or osteolytic changes are seen in the trabecular bone [7]. Immunohistochemistry with tryptase and CD117 are expressed in normal and neoplastic mast cells. The early myeloid and erythroid precursors also express CD117. The neoplastic mast cells also express CD2 and/or CD25 in addition to tryptase and CD117 [8]. Aberrant expression of these markers by flow cytometric evaluation is more sensitive and specific than histology and immunohistochemistry for detection of neoplastic mast cells [8,9]. Detection of an activating point mutation at codon 816 of c-kit by polymerase chain reaction and direct sequencing is important in the diagnosis and pathogenesis of SM [10]. Sotlar et al., [11] found that KIT D816V mutations are present in mast cells as well as in the associated hematological neoplasm component with highest frequency in CMML and less in MPN and AML. Additional cytogenetic or molecular abnormalities detected concurrently by karyotyping and/or fluorescence in situ hybridization can also be used to characterize the non mast cell lineage and support the diagnosis. When associated with AML with t (8:21)(q22:q22) translocation, cytogenetic abnormalities includes RUNX1-RUNX1T1 fusion gene [5,10].

The differential diagnosis of SM-AML is AML with mast cell hyperplasia. The latter can be diffuse, interstitial, or loosely scattered throughout the bone. These cells show round nuclei with densely granular cytoplasm. Mast cell hyperplasia can be seen in myeloid and lymphoid neoplasm as well as in toxic and inflammatory condition. The neoplastic mast cells show aberrant expression of CD2 and/or CD25 [6,12]. However, these are absent in normal mast cells. Activating c-kit mutations are also considered to be diagnostic of neoplastic mast cells. In this study, one case showed nodules of spindle shaped mast cells in the interstitium, which were positive for CD117. However CD2 or CD25 was not done in any of the cases, due to limited resources. Hence the neoplastic nature of the mast cells could not be specifically defined in this study.

Studies have shown a specific cytogenetic abnormality t (8:21) in some cases of mastocytosis associated with AML [13]. Two cases in this study also showed similar finding. AML with t (8:21) is usually associated with good response to chemotherapy with complete remission and long-term disease-free survival rate. However the prognosis is adversely affected with poor response to high dose chemotherapy when associated with mast cells. The mast cells continue to persist with standard chemotherapy regimen. The same was observed in this study and these patients were more prone to relapse. Thus awareness of this entity will help to stratify a subset of patients requiring more aggressive therapy and consideration of stem cell transplantation.

Careful evaluation of bone marrow to look for coexisting mastocytosis at the time of initial diagnosis and post induction therapy is important as the mast cells may be unapparent at initial diagnosis. This finding helps in identifying patients with increased risk of relapse or incomplete remission following therapy. Mastocytosis associated AML with t (8:21) translocation is extremely rare and carries a poor prognosis.

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