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

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
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

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Age (years)/ Gender</th>
<th>Clinical presentation</th>
<th>Flow cytometry/ Cytogenetics</th>
<th>Bone marrow at 28th day post induction and follow up</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28/M</td>
<td>Fever, weakness, shortness of breath, petechiae, anaemia and splenomegaly</td>
<td>90</td>
<td>Flow cytometry Positive Markers CD 45 CD 117 CD 34 HLA – DR Cy MP0</td>
<td>Partial Remission with 7% blasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71</td>
<td>Negative Markers CD 3 CD 4 CD 8 CD 33 CD 15 CD 14 CD 7 Cy 79a CyCD3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21/M</td>
<td>Fever, weakness, anaemia</td>
<td>40</td>
<td>Cyto genetics - t (8:21) detected</td>
<td>Complete remission</td>
</tr>
<tr>
<td>3</td>
<td>54/F</td>
<td>Fever, weakness</td>
<td>68</td>
<td>80</td>
<td>Partial remission with 14% blasts</td>
</tr>
<tr>
<td>4</td>
<td>55/F</td>
<td>Fever, malaise, shortness of breath</td>
<td>89</td>
<td>76</td>
<td>Cyto genetics - t (8:21) positive</td>
</tr>
</tbody>
</table>

Table 1: Clinicopathological features of cases of AML associated with mastocytosis at initial presentation.
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 paratrabeclar, 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-RUNXI1 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
and 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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