Acute myeloid leukemia with mast cell differentiation is characterized by interstitial mast cells, complex karyotype, TP53 alterations and poor prognosis

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Acute myeloid leukemia with mast cell differentiation is characterized by interstitial mast cells, complex karyotype, TP53 alterations and poor prognosis

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Contributions: DHK collected and analyzed the data and wrote the manuscript. SAW, WW, SL, PL, MJY, and RNM, contributed data and edited the manuscript. GT and QW analyzed the cytogenetic data. CCY analyzed the molecular data. MK treated the patients. XW collected data. LJM analyzed data and wrote the manuscript. JX designed the study, collected and analyzed the data, supervised the study and wrote the manuscript. All authors reviewed and approved the manuscript.

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Myelomastocytic leukemia (MML) is an extremely rare entity, characterized by advanced myeloid neoplasms with prominent mast cell (MC) differentiation, the latter defined arbitrarily as the presence of atypical MCs and/or metachromatic blasts ≥ 10% on bone marrow (BM) and/or peripheral blood (PB) smears. Cases of mast cell leukemia or systemic mastocytosis associated with hematologic neoplasm are excluded [1-8]. The prognosis of patients with MML is poor [1-3, 9, 10]. In our practice, we have encountered AML cases with increased MCs shown by flow cytometry immunophenotypic analysis (FCI). However, the MCs are mostly <10% of all nucleated cells, not meeting the diagnostic criteria for MML. A recent study of 9 patients with myeloid neoplasms showed 0.5% to 3% myeloblasts with MC differentiation by FCI, and the authors proposed a potential pre-MML condition [11]. However, that study is limited by its small sample size and heterogeneous leukemia types.

Among 2,167 AML cases at our institution, we identified 21 (~1%) cases of AML with MC differentiation (AML-MC), defined as: (1) increased immature MCs (>0.3%; >3SD above normal/reactive BM MCs) by FCI that are: CD117+bright, HLA-DR+low/negative, CD45+dim with low side scatter, CD38+, CD123+, CD34+partial/dim (Figure 1A); (2) cells with metachromatic granules observed on PB and/or BM aspirate smears; and (3) >1% MCs shown by tryptase immunohistochemistry in BM biopsy specimens. This study was approved by the Institutional Review Board. Our cohort included 11 men and 10 women with a median age of 68 years (range, 28-83 years). Twelve patients had a history of malignancy: 9 (43%) had myeloid neoplasms including 6 myelodysplastic syndrome, 2 chronic myelomonocytic leukemia, and 1 chronic myeloid leukemia (CML), 3 (14%) with lymphoid neoplasms, and 3 (14%) with solid tumors. Among them, 2 patients had both lymphoid and myeloid neoplasms, and 1 patient had both solid tumor and myeloid neoplasm. The classification of these AML cases is listed in
Supplemental Table 1. The myeloblasts (without MC differentiation) were mostly large, with small amounts of agranular cytoplasm (Figure 1B-D). The blasts with MC differentiation were usually small to medium-sized, with a few metachromatic cytoplasmic granules, consistent with metachromatic blasts (Figure 1B-D). Atypical immature or mature MCs that were round to oval, mostly mononuclear or occasionally bi-lobed or segmented nucleated and often with hypogranular cytoplasm, were also present. The median count of cells with metachromatic granules was 6% (range, 1-41%). Five of 18 (28%) cases had ≥10% cells with metachromatic granules, consistent with MML. Background dysplasia was present in 18 of 20 (90%) cases (Figure 1D). Dysplasia was observed in granulocytic (n=15; 75%), erythroid (n=14; 70%), and megakaryocytic (n=10; 50%) lineages and involved multiple lineages in 16 (80%) and a single lineage in 2 (10%) cases. Immunohistochemistry for CD117 highlighted myeloblasts (dim) and MCs (bright) in the BM (Figure 1F). The median MC percentage by tryptase was 5% of the BM cellularity (range, 1-40%) and the MCs were distributed in an interstitial pattern without forming aggregates. The intensity of tryptase expression in MCs was weak to moderate in most cases (Figure 1G).

Next generation sequencing (NGS) analysis using panels designed to target genes commonly mutated in myeloid neoplasms was performed on all cases (20 cases using an 81-gene panel, 1 case using a 28-gene panel). TP53 was most frequently mutated, detected in 11 of 21 (52%) cases, followed by NRAS (n=7; 33%), ASXL1 (n=4; 19%), and RUNX1 (n=4; 19%) (Figure 2A). No other gene mutations including KIT were identified. TP53 mutations identified in the AML-MC cases included nonsense (n=8), missense (n=3), and splice site mutations (n=2) (Figure 2B). Eleven of 13 (85%) TP53 mutations were present within the DNA binding domain; 2 (15%) mutations occurred in splice sites. In the 10 TP53 wild-type cases, NRAS was most often
mutated (n=4; 40%). There was no significant difference in the percentage of MCs between the
*TP53* mutant and wild-type cases (*Supplemental Figure 1A*). Thirteen of 19 (68%) cases had a
complex karyotype (*Figure 2A*). Nine of 21 (43%) cases showed *TP53* deletion by fluorescence
in situ hybridization (FISH) (*Figure 2A*). Seven of 21 (33%) cases had both *TP53* deletion and
mutation (biallelic *TP53* alterations) (*Supplemental Figure 1B*).

Ten (48%) patients were treated with intensive chemotherapy, with or without targeted therapy.
Seven (33%) patients received hypomethylating agents with or without venetoclax. Two (10%)
patients were treated with immunomodulator therapy alone and 1 (5%) was treated with targeted
therapy alone. Three (14%) patients received allogeneic stem cell transplant (SCT). After a
median follow-up of 7.4 months (range, 0.2-41.9 months), 13 of 21 (62%) patients died, with a
median overall survival (OS) of 9.6 months (*Figure 3A*). Patients of 65 years old or older had a
significant shorter OS than those younger than 65 years (*Figure 3B*). The percentage of MCs
did not affect OS, using a cut-off value of 5% (*Figure 3C*), 2% or 10% (data not shown). The
OS of AML-MC patients showed no difference after stratifying patients by *TP53* mutation status
(mutated vs. wild-type) (*Figure 3D*). Patients with a non-complex karyotype or those who
received SCT tended to show a better OS than patients with a complex karyotype or without
SCT, but these differences did not reach statistical significance (*Figure 3E-F*).

Our definition of AML-MC is very similar to the “pre-MLL condition” described by Panda et al
[11]. MML requires that MCs comprise \( \geq 10\% \) of BM cells, an arbitrary and stringent cut-off
that is likely set too high; as a result only about 10 cases have been reported in the literature [1-7].
Similar to MLL, the MCs in AML-MC were interstitially distributed in the background of
dysplasia. These MCs are immunophenotypically immature, in contrast to the mature MCs
(negative for CD34, brighter CD45, higher SSC) as can be seen in chronic lymphocytic leukemia
and reactive conditions (data not shown). Among the 9 AML-MC patients with a history of myelodysplastic and/or myeloproliferative neoplasms, 5 cases of the earlier neoplasms were assessed by FCI and none showed increased immature MCs. Tryptase is often strongly expressed on mature MCs, but can be decreased or lost in MML and mast cell leukemia [8, 12], thought to be attributable to the MC immaturity. Low tryptase expression on immature MCs is also seen in AML-MC cases, supported by their immunophenotypic signature and decreased tryptase staining. Interestingly, elevated serum tryptase level were reported in MML cases and some patients had symptoms due to inappropriate release of MC mediators [1, 6-8, 13]. None of AML-MC patients we report were tested for serum tryptase or had mediator-related symptoms. Although little is known about the genetic and molecular pathogenesis underlying MML, a complex karyotype is found in 75% of cases [1-4, 8-10, 13, 14]. In this cohort of AML-MC cases, about 70% showed a complex karyotype and 50% had TP53 deletion. One case (5%) had t(8;21) which has been reported in MML [1, 5, 6]. We also had two (10%) AML-MC cases with inv(16), which has not been previously reported in MML. Another recurrent genetic abnormality was t(9;22), seen in two (10%) BP-CML cases. CML in accelerated/blast phase has been reported to develop MML or to have increased immature MCs [2, 11]. KIT mutations are observed in approximately 20-40% of core binding factor (CBF) AML cases, but they are typically not detectable in MML as was observed in this cohort [4, 8, 13, 14]. TP53 was the most frequently mutated gene, occurring in about 50% of AML-MC cases, and 64% of the TP53-mutated cases had biallelic inactivation (one copy mutated, the other copy lost). However, there was no significant difference in the percentage of MCs between TP53 mutant and wild-type cases, suggesting that TP53 is not a driver for MC differentiation.
The prognosis of AML-MC patients was poor, with a median OS of 9.6 months, similar to OS reported in MML patients [1-3, 9, 10]. Patient outcome was even worse if they were 65 years or older. Generally, AML with t(8;21) and inv(16) are associated with a favorable prognosis [15]. In the current study, after initial diagnosis, the patient with t(8;21) died in 17 months and one of two patients with inv(16) died in 4 months, both due to infection and respiratory failure. The sample size of CBF AML-MC cases in this study is too small to assess their behavior. The patients with a non-complex karyotype or if they received SCT tended to show a better OS than patients with a complex karyotype or without SCT, but these differences did not reach statistical significance, possibly also due to the small sample size. SCT was reported to attain prolonged survival in two MML with t(8;21) patients [1, 6]. The percentage of MCs in AML was not associated with OS, using a cut-off value of 2%, 5%, or 10%, suggesting that once the immature MC component is increased, arbitrarily setting a MC% cut-off may not be relevant.

In summary, patients with AML-MC are characterized by interstitial MCs, multilineage dysplasia, complex karyotype, TP53 alterations, and poor prognosis. The results of this study support recognition of this rare subset of aggressive AML cases, which are not adequately captured by current prognostic systems.
References


Figure legends

Figure 1. A representative case of acute myeloid leukemia with mast cell differentiation (AML-MC). A, The MCs are positive for CD117 (bright), CD45 (dim), CD38, CD123, CD34 (partial/dim), CD13 (partial), and are negative for HLA-DR, with low side scatter, consistent with immature MCs. B-D, the peripheral blood (B) and bone marrow aspirate smears (C-D) reveal myeloblasts (red arrow heads) which are large, with irregular nuclear contour, fine chromatin, inconspicuous nucleoli, and a small amount of agranular cytoplasm. Metachromatic blasts (green arrow heads) have a small to moderate amount of cytoplasm containing a few metachromatic granules. Erythroid dysplasia is present in the background (black arrow). E, the bone marrow biopsy shows a hypercellular marrow (~100% cellularity) with markedly increased blasts. F-G, immunohistochemical stains for CD117 (strong, F) and tryptase (weak, G) highlight scattered MCs. CD117 also stains the myeloblasts (dim, F). B-D, Wright-Giemsa stain, x1000. E, hematoxylin-eosin stain, x400 (D). F-G, immunohistochemistry, x400 (F), x600 (G).

Figure 2. The molecular and cytogenetic findings of acute myeloid leukemia with mast cell differentiation (AML-MC). A, the oncoplot of gene mutations and status of karyotype and TP53 deletion. B, the lollipop graph of TP53 mutations in AML-MC (template from Uniprot).

Figure 3. The overall survival (OS) of patients with acute myeloid leukemia with mast cell differentiation (AML-MC). A, in all 21 patients with AML-MC. B, in patients with age ≥65 years and <65 years. C, in patients with ≥5 % MCs and <5 % MCs. D, in patients with mutated and wild-type TP53. E, in patients with a complex karyotype and non-complex karyotype. F, in patients with and without allogeneic stem cell transplant (SCT).
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<td>Complex Karyotype</td>
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<td>TP53 deletion</td>
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Colours:
- Red: Positive
- Green: Internal tandem duplication
- Blue: Double mutations
- Grey: Negative

### Fig. 2B

- **K motif**
- **Bipartite nuclear localization signal**
- **DNA binding domain**
- **Nuclear export signal**
- **TADI**
- **TADII**

**Frequency** vs **Amino acid number**

- **Missense mutation**
- **Nonsense mutation**
- **Splice site mutation**

**Key:**
- c.560-2A>T
- c.994-2A>C
Fig. 3

A. All patients (n=21)

B. Probability of Survival
- Age >=65
- Age <65
p=0.005

C. Probability of Survival
- Mast cell <5%
- Mast cell >=5%
p=0.90

D. Probability of Survival
- Mutated TP53
- Wild type TP53
p=0.53

E. Probability of Survival
- Complex karyotype
- Non-complex karyotype
p=0.15

F. Probability of Survival
- SCT
- No SCT
p=0.17
Supplemental Table 1. Classifications of Acute Myeloid Leukemia with Mast Cell Differentiation

<table>
<thead>
<tr>
<th>AML classification</th>
<th>Entire cohort (n =21)</th>
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<tbody>
<tr>
<td><strong>WHO classification (5th edition)</strong></td>
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<tr>
<td>AML with RUNX1::RUNX1T1 fusion</td>
<td>4.8% (1/21)</td>
</tr>
<tr>
<td>AML with CBFB::MYH11 fusion</td>
<td>9.5% (2/21)</td>
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<tr>
<td>Acute myelomonocytic leukemia</td>
<td>4.8% (1/21)</td>
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<tr>
<td>Myeloid neoplasm post cytotoxic therapy</td>
<td>24% (5/21)</td>
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<tr>
<td>AML, myelodysplasia-related</td>
<td>48% (10/21)</td>
</tr>
<tr>
<td>BP-CML</td>
<td>9.5% (2/21)</td>
</tr>
<tr>
<td><strong>ICC classification</strong></td>
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</tr>
<tr>
<td>AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1</td>
<td>4.8% (1/21)</td>
</tr>
<tr>
<td>AML with inv(16)(p13.1q22)/CBFB::MYH11</td>
<td>9.5% (2/21)</td>
</tr>
<tr>
<td>AML with myelodysplasia-related gene mutations</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>AML with myelodysplasia-related cytogenetic abnormalities</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>AML with mutated TP53</td>
<td>48% (10/21)</td>
</tr>
<tr>
<td>BP-CML</td>
<td>9.5% (2/21)</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; BP-CML, blast phase of chronic myeloid leukemia.
Supplemental Figure 1. A, the number of mast cells in AML-MC with mutated and wild-type TP53. B, status of TP53 mutation and deletion in AML-MC cases. AML-MC, acute myeloid leukemia with mast cell differentiation.