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Molecular Insight Story

Systemic mastocytosis with an associated hematological neoplasm (acute myeloid leukaemia with RUNX1::RUNX1T1 fusion) – A case study

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ABSTRACT

Systemic mastocytosis (SM) is a rare blood disorder that can affect multiple body organs. There are some patients of SM with coexpression of hematological neoplasm designated in the World Health Organization classification as SM with an associated hematological neoplasm (SM-AHN). A 13-year-old female was referred for immunophenotyping since blasts were reported in the bone marrow aspirate. On performing flow cytometry, abnormal myeloid blasts (>20%) were obtained on flow cytometry suggestive of acute myeloid leukemia with aberrant expression of CD19. Furthermore, there were increased mast cells abnormally expressing CD25. The aspiration slides reviewed showed atypical mast cells Type I and Type II. Molecular analysis revealed RUNX1::RUNX1T1 fusion as well as KIT D816V mutation. Karyotyping revealed a three-way translocation involving chromosomes 8, 12, and 21 consistent with RUNX1::RUNX1T1 fusion. Fluorescence in situ hybridization (FISH) performed using a dual color dual fusion probe for RUNX1::RUNX1T1 showed atypical abnormal pattern consistent with RUNX1::RUNX1T1 fusion. This rare diagnosis could be reached as a result of a strong correlation between morphology, immunophenotyping, cytogenetics, and molecular analysis, leading to a better treatment plan for the patient.

Keywords: Systemic mastocytosis, AML with RUNX1::RUNX1T1, KIT D816V

INTRODUCTION

Mastocytosis is classified into three types based on the tissue affected: (1) Systemic mastocytosis (SM), (2) cutaneous mastocytosis (SM), and (3) mast cell sarcoma.[1] Patients with SM have different clinical behavior and prognosis. The World Health Organization (WHO) classification (2017) identified this by subdividing this entity into five distinct subgroups; indolent systemic mastocytosis, smoldering systemic mastocytosis, SM with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis, and mast cell leukemia.[2] Around 20–30% of cases of SM have a second hematologic disease with the clonal myeloid disorder being very common.[3] SM with acute myeloid leukemia presents the worst prognosis.[4] We present a case of mastocytosis associated with acute myeloid leukemia (AML) and discuss the correlation between clinical

features, bone marrow findings, immunophenotyping, cytogenetics, and molecular analysis.

CASE REPORT

A 13-year-old female presented in a tertiary care hospital in January 2021 with complaints of fever on and off for 20 days associated with left-side earache and dimness in vision. On evaluation, mild pallor was evident (otherwise clinically well). The systemic evaluation was suggestive of mild hepatosplenomegaly (and no other abnormalities). On blood investigations, complete blood count was suggestive of leukocytosis with 25% blast cells and thrombocytopenia. The coagulation profile was within normal limits. She was referred for immunophenotyping. Morphology in the bone marrow showed blasts with abundant basophilic cytoplasm, perinuclear clearing, and a single long and sharp Auer rod [Figure 1]. Granulocyte precursors with abnormal cytoplasmic staining were also seen. Flow cytometry (performed using BD FACS CANTO II) was suggestive of acute myeloid leukemia with aberrant expression of CD19 [Figure 2]. Blasts showed dim to moderate CD45, low to intermediate systemic sclerosis (SSc), dim to moderate CD33, dim to moderate CD13, dim-mod CD117, dim to moderate CD38, moderate to bright CD34, moderate to bright human leukocyte antigen – DR isotype (HLADR), and dim CD19 and positive CD56. Furthermore, there were increased mast cells abnormally expressing CD25 [Figure 3].

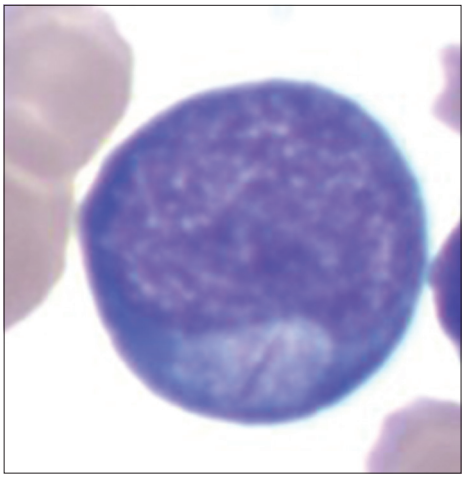

Figure 1: Blast with abundant basophilic cytoplasm, perinuclear clearing, and single long and sharp Auer rod.

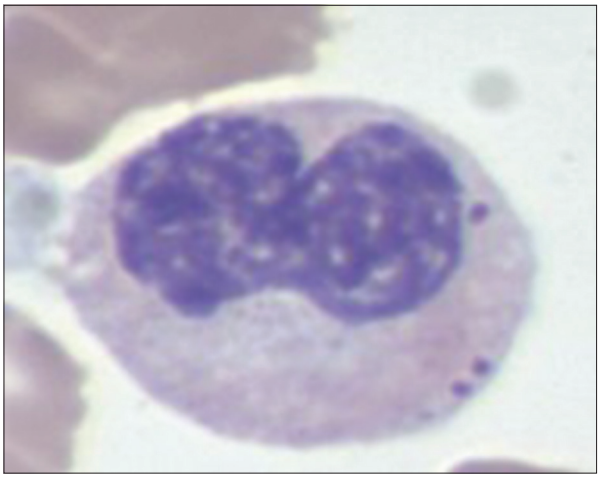

Figure 2: Granulocyte precursor with abnormal cytoplasmic staning.

The aspiration slides reviewed showed atypical mast cells Type I with decentralized nuclei and Type II, also referred to as promastocyte (with bilobed nuclei) [Figures 4 and 5].

Karyotyping showed a three-way translocation involving chromosomes 8, 12, and 21 consistent with RUNX1::RUNX1T1 fusion. FISH was also performed using a dual color dual fusion probe for RUNX1::RUNX1T1 which also showed atypical abnormal pattern consistent with RUNX1::RUNX1T1 fusion [Figures 6 and 7].

Next-Generation Sequencing (NGS) was performed on Ion-Torrent machine using the Ampliseq library preparation kit both for deoxyribonucleic acid and ribonucleic acid and sequenced on the Ion Torrent S5 Prime sequencer. The analysis was performed on Ion Reporter software which showed the RUNX1::RUNX1T1 fusion (Read counts per million - 88809) in RNA sequencing and KIT D816V mutation (variant allele frequency [VAF]: 40.18%) in DNA sequencing [Figures 8 and 9].

She was planned for Induction chemotherapy with a (3 + 7) regimen which she tolerated well.

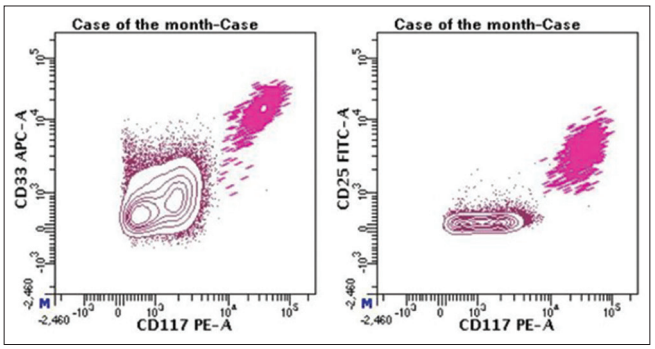

Figure 3: Images show mast cells (gated as magenta) which abnormally express CD25.

Post-induction sample minimal residual disease was positive with immunophenotyping showing 0.448% residual disease expressing abnormal immunophenotype similar to that present at diagnosis. In addition to this, 8.36% of events

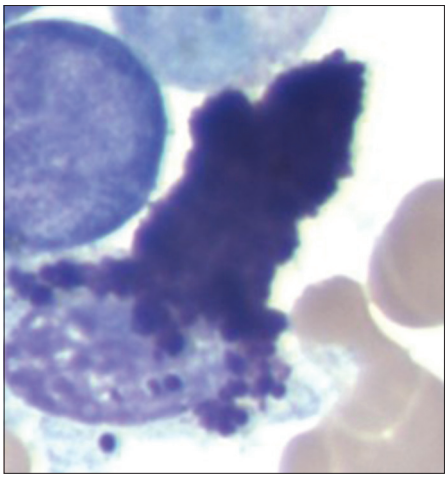

Figure 4: Atypical spindle-shaped mast cells Type I with decentralized nuclei.

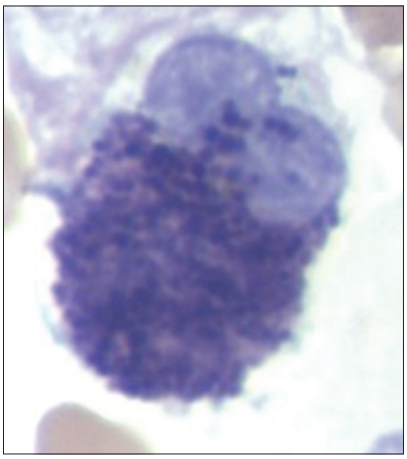

Figure 5: Atypical mast cell Type II, also referred to as promastocyte with bilobed nuclei.

could be gated which expressed immunophenotype of mast cells expressing CD25. DNA and RNA sequencing showed the presence of the same mutation KIT D816V (VAF: 2.72%) and fusion RUNX1::RUNX1T1 (Read counts per million: 19053)

She was further consolidated with three cycles of high dose Cytarabine 3 g/m^2 D1,2,3 q28 days. Post-completion of treatment, she was on follow-up till August 2021 following which she relapsed and unfortunately succumbed to her illness in December 2021.

DISCUSSION

There are very few case studies as a part of a small series on SM with an associated hematological neoplasm (acute myeloid leukemia with RUNX1::RUNX1T1 fusion) Furthermore, SM is rare in the pediatric population.[4,5] The accurate incidence of SM coexisting with RUNX1::RUNX1T1 fusion AML is unknown. However, some reports mention, the possibility of missing this diagnosis due to the excess number of blast cells and the tendency of mast cells to localize within the stroma of bone marrow particles.[6,7]

The WHO (2017) states one major criterion and four minor criteria for the diagnosis of SM. The case in discussion satisfied at least three minor criteria with >25% of all mast cells in bone marrow aspirate being immature or atypical, the presence of D816 activating point mutation in KIT in bone marrow, and mast cells in bone marrow expressing CD25 in addition to normal mast cell markers.[8]

Most cases of SM-AHN are associated with myeloid neoplasm. The most common being chronic

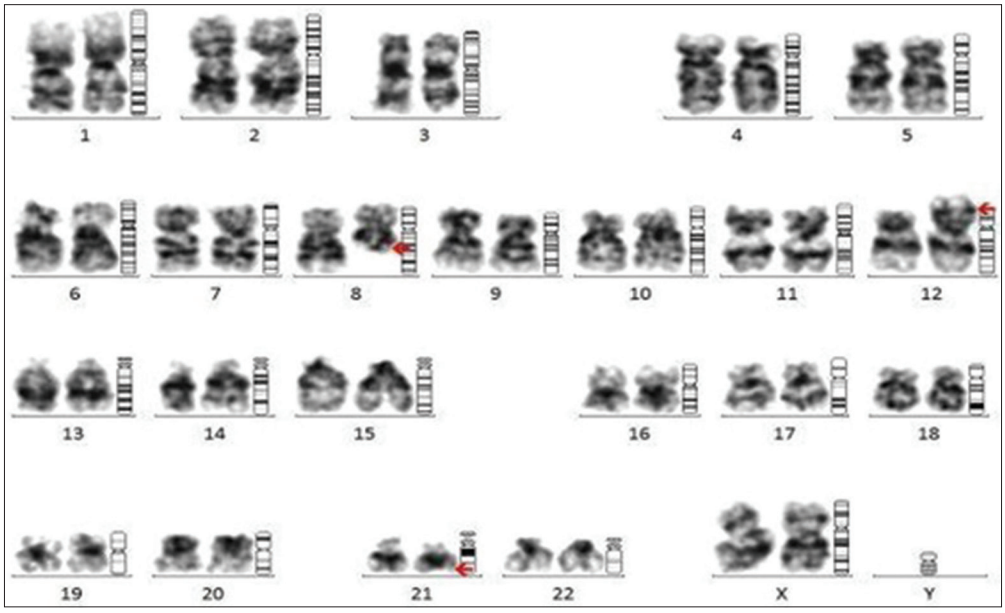

Figure 6: Karyogram: 46,XX,t (8;12;21) (q22;p13;q22).

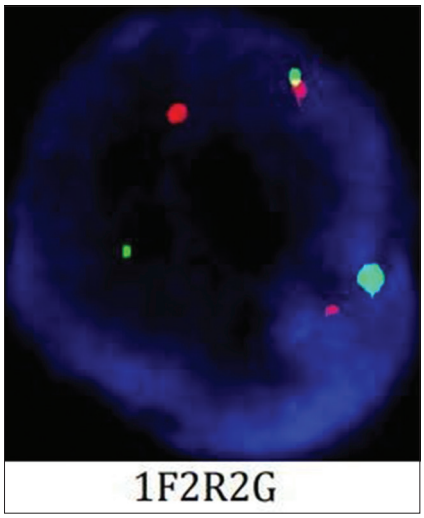

Figure 7: FISH image showing RUNX1::RUNX1T1 fusion.

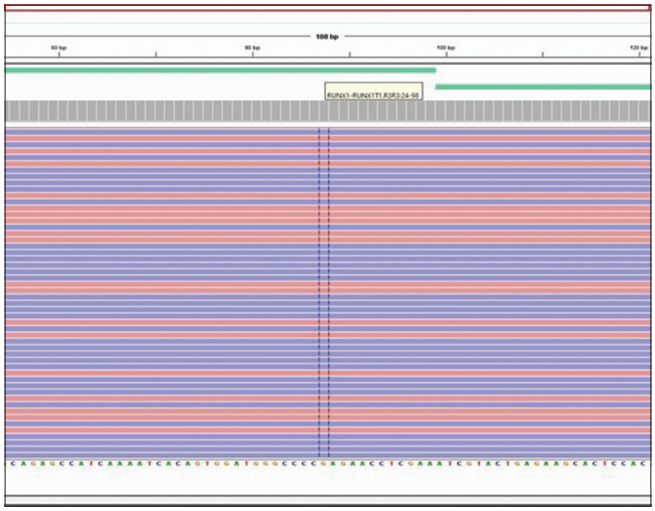

Figure 8: Molecular analysis revealed RUNX1::RUNX1T1 fusion.

myelomonocytic leukemia (CMML) followed by myelodysplastic syndrome, myeloproliferative neoplasms, AML, and ph-chromosome negative or atypical chronic myeloid leukaemia.[9] Patients presenting with SM-AML have the worst prognosis.[10]

The presence of KIT D816 mutation is seen in >90% of cases of SM.[1]

Because of the particularly poor prognosis of this subgroup, a vigilant morphologic evaluation of peripheral blood smears and bone marrow remains important for the early detection of the disease and subsequent timely treatment.

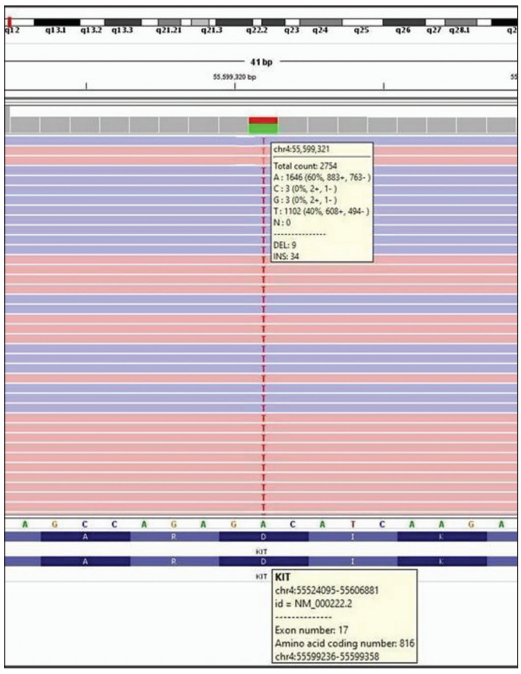

Figure 9: Molecular analysis revealed KIT D816V mutation.

QUIZ CORNER

1. Most cases of SM-AHN are associated with myeloid neoplasms. The most common association is with –
   a. myelodysplastic syndrome,
   b. myeloproliferative neoplasms,
   c. chronic myelomonocytic leukemia (CMML)
   d. AML
2. Which mutation is seen in >90% cases of SM
   a. MYD88 L265P
   b. IDH 132H
   c. KIT D816
   d. KRAS G12D
3. Which marker is abnormally expressed by mast cells
   a. Tryptase
   b. CD 25
   c. CD 117
   d. CD 34

To see the quiz answers, please scan the QR code below

CONCLUSION

SM associated with AML (RUNX1::RUNX1T1) is extremely rare and carries a dismal prognosis. During the evaluation of t (8;21) (q22;q22) AML, care should be taken to look for coexisting SM in the initial and subsequent bone marrow specimens since the mast cell infiltrate may be subtle and easily overlooked. This will help identify a subset of t (8;21) AML patients with a particularly poor prognosis. Thus, the correlation between different techniques helps for better clinical management and treatment modalities.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflict of interest

There are no conflict of interest.

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