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Case Report
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Pediatric Systemic Mastocytosis in Association with Clonal Non-Mast Cell Lineage Hematopoietic Neoplasm: A Case Report and Literature Review

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Abstract

Systemic mastocytosis associated with clonal non-mast cell lineage hematopoietic neoplasm (SM-AHM) (usually myeloid) is sporadically reported to occur in both adults and elderly population. Occurrence of SM-AHM in pediatric population (≤ 14 years) is rarely reported with paucity of data pertaining to its biological behavior and therapeutic outcome. We described a case of SM in association with t (8; 21) (q22; q22) positive Acute Myeloid Leukemia (AML) in a young child with negative KIT D816V mutation with characteristic bone marrow morphologic and immunophenotypic features and unfavorable outcome following intensive chemotherapy. We also presented a comprehensive review of similar cases in pediatric population to highlight the morphologic, molecular, and biological behavior of such potentially unfavorable disease.

Keywords: Mastocytosis; Acute myeloid leukemia; Cytogenetics; KIT; Prognosis

Introduction

Mastocytosis comprises a heterogenous group of disorders characterized by infiltration of abnormal mast cells in different organs or tissues driven by constitutive activation of KIT receptor. Although a somatic point mutation involving codon 816 of KIT gene (KIT D816V) is the most common underlying molecular event (>90% cases), activating mutations involving the extracellular, transmembrane, or juxtamembrane domains are reported in <1% of advanced SM [1]. An associated clonal non-mast cell lineage hematological malignancy (SM-AHM), usually myeloid, is rarely reported in such entities [2]. Occurrence of SM-AHM in pediatric population is very rarely reported in the literature compared that in adults or elderly population; the biologic behavior of which is largely unknown [3-5]. In this manuscript, we aimed to describe a case of SM-AHM in a young child with clinico-morphological, immunophenotypic, cytogenetics/molecular characteristics, and therapeutic outcome with a comprehensive review of similar published reports in the literature.

Case Presentation

A 14-year-old male, born out of non-consanguineous parents and no prior co-morbidities, presented with a two-month history of moderate grade fever, dry cough, petechiae and purpuric spots all over the body with one bout of hemoptysis. Symptoms gradually progressed over a month when the child presented to a local hospital where he had received two units of blood transfusion and four units of platelet transfusion for anemia and thrombocytopenia 14 days prior to present hospitalization. General and physical examination revealed significant conjunctival pallor, no scleral icterus, petechiae all over the body, and hepatosplenomegaly (liver 7 cm and spleen 3 cm below right and left costal margin, respectively), but no sternal or bony tenderness or significant lymphadenopathy.

His routine Complete Blood Count (CBC) along with examination of peripheral blood smear revealed normocytic normochromic anemia [hemoglobin; 35 g/L (ref. 120-140 g/L), mean corpuscular volume; 85 fL, corrected reticulocyte count; 0.5% (ref. 0.5-1.2%)], leukocytosis (total leukocyte count; 15 × 10^9/L (ref. 4-11 × 10^9/L) with 60% myeloid blasts, 5% myelocytes, 25% stab and segmented neutrophils, 10% lymphocytes, and severe thrombocytopenia (platelet count; 5 × 10^9/L (ref. 150-450 × 10^9/L), thus consistent with a diagnosis of Acute Myeloid Leukemia (AML). Peripheral blood flowcytometry revealed that these blasts expressed CD34, CD117, cyMPO, HLA-DR, CD38, CD13, and CD33 with aberrant co-expression of CD19 and CD58.

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Table 1: Clinicopathological, immunophenotypic and molecular/cytogenetic characteristics, therapeutic and outcome data of pediatric systemic mastocytosis associated with acute myeloid leukemias.

Sl. no.	Age, gender	Presentation	Hb (g/L)	TLC (×10⁹/L)	Plt (× 10⁹/L)	PS/BM Blast (%)	Blast phenotype (FC/IHC)	Cytogenetics	Mast cell phenotype	Presentation (%)	C-KIT mutation	Architecture	Morphology	Granules	Therapy	Follow up	Authors, year, ref.
1	10y, M	Abdominal pain, fever, Spleen. skin; normal	39	28	5	-/61%	CD34, CD117, CD13, CD33, HLA-DR, MPO	t (8;21) (q22; q22)	CD45+, CD117+, Tryptase+, CD33+, CD34-, CD2-, CD25-	Post induction (57%)	D816V-	Diffuse	Round, blastoid, type I	Hypogranular	I-Cy, Dn, Etp, Con-Cy, Mit	Remission (3months), Relapse (9months), Death (9 months) (38% blasts, 20% mast cells)	Mahadeo, 2011 (57 ng/ml)
2	2.5y, F	Epistaxis, blood in stool, edema, Liver and spleen	35	9.2	9	4%/11%	AML (CD34, CD117)	Not described	CD117, Toluidine Blue	Concurrent	Not done	Clusters	Spindle/ fusiform	Hypogranular, uneven granularity	Symptomatic	Death, 2months	Sharma, 2011
3	3y, F	Erythmatous papules, fever, Epistaxis, L, Spleen	50	26	10	-/20%	CD13, CD33, MPO, CD117	Normal	CD25, CD117	Concurrent (>25%)	D816V-	Paratrabecular	Spindle, type I	Dense	Supportive	Death, 24 h, Mast cell infiltration of liver	Gogia, 2013 Tryptase; 57 ng/ml
4	5y, F	Fever, Joint pains	NA	12.4	NA	55%/70%	CD34, HLA-DR, CD13, CD33	t (8;21) (q22; q22)	CD25	Concurrent (18%)	D816A+	Clusters and aggregates (>15)	Spindle, type 1	Hybrid granules	Etoposide, Cytarabine, mitoxantrone	Remission (2 months), relapse (4 months), Death due to progressive AML	Yabe, 2012
5	14y, M	Occult, Skin; normal	NA	NA	NA	ND	FAB M1	t (8;21)	CD117, CD2, CD25, CD45 (moderate), CD33, CD68 (FC)	Concurrent	D816A+					Remission with persistence of MC (5 months)	
6	14y, F	Abdominal pain, fever, weakness, limb numbness, skin; normal	40	11	5	66%/68%	CD45, CD34, CD117, CD13, MPO	AML1-ETO (>90%) (FISH)	CD117, CD2, CD25; +, CD34-	Concurrent >25%	Not done	Aggregates (>15) Perivascular aggregates, paratrabecular	Spindle	Hypogranular	3+7 (cytarabin + daunorubicin)	Persistence of MC Partial molecular response AML1-ETO (8%)	Meyran
7	7y, F	Fever, Abdominal distension, weakness, petechial rash Spleen	72	34	30	24%/70%	CD45 (dim), CD34, HLA-DR, CD13, CD19 (heterogenous), CD33 and CD38 (moderate) c MPO, CD56 (weak)	AML1/ETO (RUNX1T1/ RUNX1)	High scatter bright CD117, CD25, CD33+, dim CD2, HLA-DR/ CD123-	Concurrent	D816V-	Dense aggregates	Oval to spindle	Densely granular	Cytarabine (1m); Cyt Ara + Dauno +Etp (2m); Cyt Ara + Dauno +Etp (3m)	No remission (1 month) MRD+ (3 months) MRD- (7 months) Persistence of MC throughout	Gadage
8	NB/M	Skin lesions present HSM	-	-	Low		CD117, CD25 and CD30 (skin Bx)	No leukemia related pattern	CD25, CD117, CD30	Negative (BM)	D816V+ (skin and BM)	>15	Spindle	Not described	Vincristine, dasatinib and cladribine	Death Congenital aggressive systemic mastocytosis	Rabade 2016
9	13y, M	Rt. tonsilar, scapular, LN mass, lung involvement psoriasis Spleen	WNL	WNL	WNL	16%/69% Blasts with vacuolated cytoplasm and metachromatic granules	Positive (FC) for HLA-DR, CD56, CD33, CD117, BDCA-1, CD9, CD69, CD11c, and CD11b; NEGATIVE for CD34, CD123, CD25, CD2 and MPO	47, XY, + 5, t (1; 9). Leukemia related fusion genes; negative	CD45, CD117	Concurrent	Not detected (exon 8, 9, 13, 17 of KIT gene) D816V-	Diffuse sheets	Blastoid	Sparse, metachromatic	Fludarabine, cytosine arabinoside, dasatinib and daunorubicin x 3 cycles Allogenic BMT	CR – Relapse (7 months), death (18 months) from presentation De novo MCL	Huang Tryptase; 64 Serum tryptase (ref; 2-10 ng/ml)
10	9y, M	Diplopia, periorbital swelling, proptosis				21%/>20%	AML	t (8:21) (q22; q22)	Not described	Concurrent	+ Asp816Tyr+	>15 (clusters)	ND	ND	cytarabine, daunorubicin, etoposide, mitoxantrone, L-asparaginase, and the anti-CD33 antibody gemtuzumab (Mylotarg)	CR, 6months	Zheng

11	10y, F	No skin involvement	116	8.4	49	-/30%	HLA-DR, CD34, TdT, CD13, CD33	t (8,1,21) (q22; p32; q22) (M2) RUNX1/ RUNX1T1	Toluidine blue, CD 2, CD25, CD117, tryptase; +	Concurrent 0.6%	- c-KIT- Residual mast cells	>15 (multifocal)	Spindle	Faint-dense	AD- (cytarabine, Daunorubicin)	Remission, gradual decline of MCs, 115 months	Jeong (data unpublished)
12	8y, F	NA	NA	NA	NA	-/30%	HLA-DR, CD34, CD13, CD33, CD19	t (8;21) (q22; q22), del (7) (q31), 45, idem,-X [7] RUNX1 / RUNX1T1	CD2, CD117, tryptase; +ve CD25; NA	Concurrent 15.6%	+ c-KIT+	>15	Spindle-Polygonal	Faint-dense	AD	Death Residual Mast cells 10 months	Won.
13	17y, F	NA	80	12.5	74	-/44%	CD34, CD13, CD117, CD33, CD19	t (8;21) (q22; q22)	CD2, CD25, CD117	Concurrent, 4.6%	+ Residual Mast cells	>15	Spindle-Polygonal	Faint-dense	AI-(cytarabine, Idarubicine)	12 months	Won.
14	6y, F	NA	90	36.7	31		CD34, CD13, CD117, CD33, CD56	t (8;21) (q22;q22) RUNX1 / RUNX1T1	CD2, CD25, CD117, Tryptase; +	Concurrent, 0.4%	- c-KIT-	>15	Spindle-Polygonal	Faint-dense	AD	28 months Death due to GVHD post ASCT	Won.
15	3y, M	Fatigue, fever, Proptosis, mass in cranial fossa	ND	173k	ND	70%/56%	CD13+, CD117+, CD34+, CD19+, MPO	t (8;21) (q22,q22)	Dim (CD117, CD2, CD25) CD9, CD33 CD22, CD25, CD2, CD69 Tryptase	Post induction, 13%	D816V was not detected	Diffuse sheets	Atypical	Not available	Not available	Not available	Won.

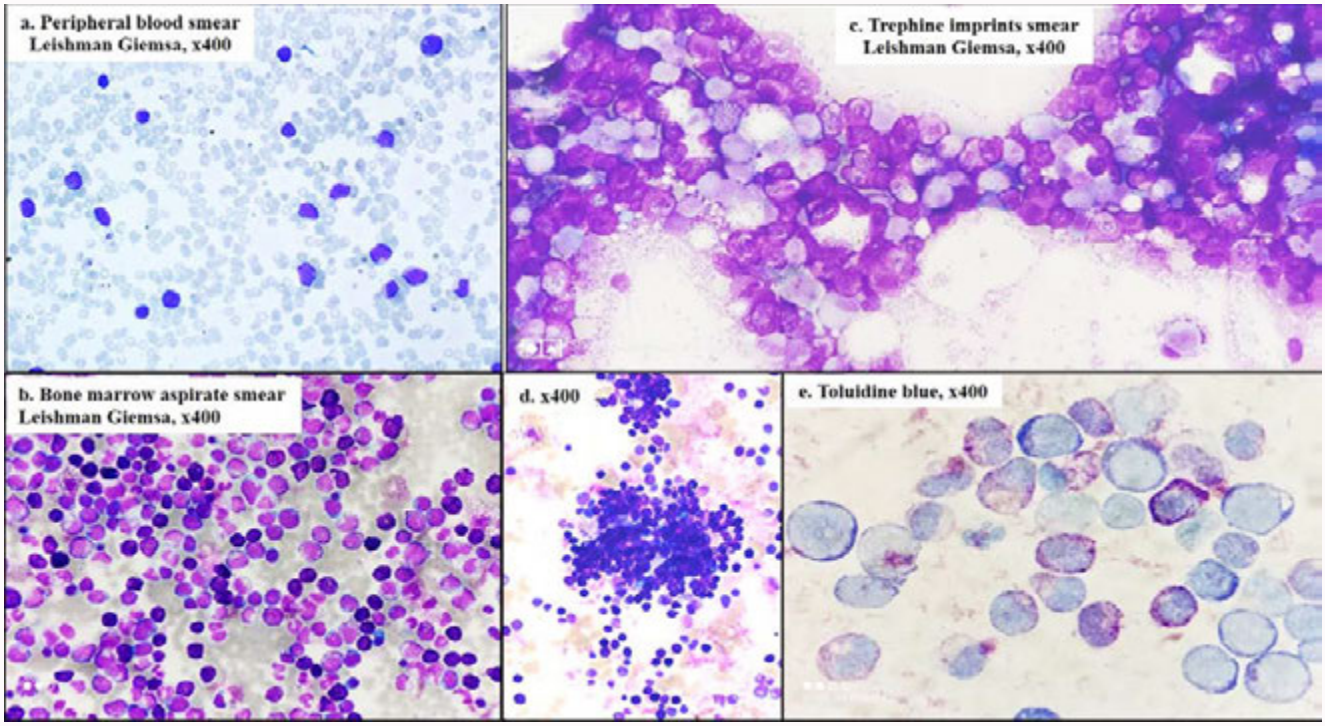

Figure 1: Peripheral blood smear in the index case showing increased population of myeloid blasts (>50% of differential count) consistent with a diagnosis of acute myeloid leukemia (a). b-d; bone marrow aspirate smears depicting dual population of intermediate size myeloid blast (pale nuclei) and scattered, increased population of mast cells (darker cells) (b). Note the localized multifocal clustering of abnormal mast cells with bilobed nuclei, showing degranulation as well as variable cytoplasmic granularity (c and d). These mast cells were highlighted by metachromatic staining such as Toluidine blue (e).

Bone Marrow (BM) aspirate smears from right iliac crest were hypercellular for age with suppressed hematopoiesis with 50% intermediate size myeloid blasts and 15% maturing myeloid lineage cells, thus suggestive of Acute Myeloid Leukemia (AML) with Maturation (FAB M2 phenotype). In addition, there were increased number of mast cells arranged dispersedly and in multifocal clusters (15% of marrow nucleated cells). These cells displayed round to polygonal in shape with moderate to abundant basophilic granules partially obscuring the round to bilobed nuclei. These cells stained negative for Myeloperoxidase (MPO) but positive for toluidine blue staining (Figure 1a-1e). Bone marrow trephine biopsy revealed marked hypercellularity for age (>90%) with interstitial infiltrates and small clusters of myeloid blasts admixed with sheets, multifocal clusters, and at places, perivascular and paratrabecular aggregates of mast cells with perinuclear cytoplasmic clearing (pseudo fried egg appearance) and round to folded nuclei with inconspicuous nucleoli. On Immunohistochemistry (IHC), the blasts were strongly positive for CD34 and MPO, weakly for CD117 whereas the mast

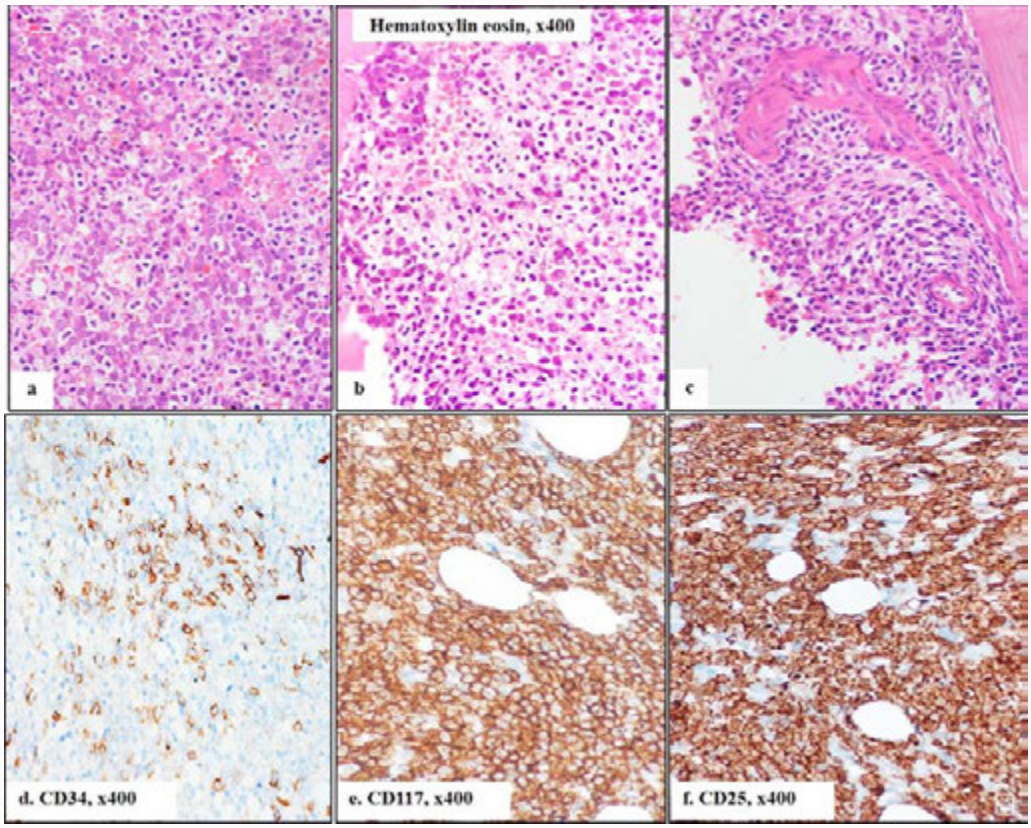

Figure 2: Bone marrow trephine biopsy from the index case showing hypercellular marrow with interstitial clusters and infiltrates of mononuclear round cells (blasts, a) admixed clusters and multifocal aggregates of cells with moderate to abundant clear cytoplasm and folded/bilobed nuclei giving a 'pseudo-fried egg' appearance (a, b). These cells at places formed perivascular swirling like pattern of arrangement (c). On immunohistochemistry, the blasts were positive for CD34 (d), CD117 and MPO (not shown). Note the diffuse and strong membranous pattern of positivity for CD117 (e) and CD25 (f) confirming the neoplastic mast cell infiltrates (Peroxidase-anti-peroxidase).

cells were strongly and diffusely positive for CD117 (membrane), CD25 (membrane), and focally for CD2 (Figure 2a-2f). Marrow cyto-histomorphology in correlation with immunophenotypic findings (both flow and IHC) were consistent with systemic mastocytosis in association with AML (SM-AML). Conventional G-banded cytogenetics and reverse transcript-polymerase chain reaction performed on bone marrow aspirate sample detected t (8;21) (q22; q22) and AML1-ETO (RNUX1-RUNX1T1) fusion transcripts, respectively (Figure 3).

The patient was started on chemotherapy as per United Kingdom Medical Research Council AML protocol (7 days cytarabine at 100 mg/m^2, 3 days of daunorubicin at 60 mg/m^2, Etoposide for 5 days at 100 mg/m^2) with triple intrathecal (cytarabine, methotrexate, hydrocortisone) therapy with blood products transfusion. Patient tolerated the induction therapy well without any grade 3 or 4 adverse events, although the patient had an episode of febrile neutropenia on day 22. The blood culture revealed growth of *Pseudomonas aeruginosa* which was treated as per antibiotic sensitivity with meropenem and vancomycin. Follow-up CBC and BM analysis performed on day 31 post-induction chemotherapy revealed normalization of peripheral blood counts, disappearance of myeloid blasts in the marrow, but with persistence of neoplastic mast cells (50% of marrow nucleated cells). KIT D816V mutational analysis performed on peripheral blood sample at the time of follow up marrow evaluation was negative.

The second induction was given after 36 days of 1st induction. The course was complicated with grade 3 neutropenic enterocolitis with *Stenotrophomonas maltophilia* sepsis, which was managed conservatively with sensitive antibiotics and patient recovered completely. First high dose cytarabine consolidation was started 38 days after the second induction at 3 g/m^2. Patient however developed fever on day 6 post-consolidation. Clinical parameters progressively worsened thereafter and he was tested positive for SARS-CoV-2. He was started on inotropic support and was shifted to ICU and intubated in view of respiratory distress. Unfortunately, patient succumbed on day 15 post-HiDAC.

Discussion

A comprehensive review of literature highlighting the sporadically reported cases of SM-AML in pediatric population is presented in Table 1 [6-14]. These included six males and nine females ranging from new born to 14 years of age. Notably hepatosplenomegaly with or without lymphadenopathy associated with peripheral blood cytopenia (s) secondary to AML dominated the clinical presentation and skin manifestations pertaining to mastocytosis were not described in any of the cases. Infiltration of clonal mast cell in BM was concurrent to AML diagnosis in 12/15 cases and two had mastocytosis diagnosis post induction, and no infiltrate was reported in one case [6,11,14].

Clonal mast cells ranged from <5% to >25% in the reported cases which showed dysplastic morphological pattern in the form of oval to spindled/fusiform shape, few mimicking blasts, and presence of variable intensity metachromatic granules. Architecturally, these mast cells formed multifocal dense clusters (>15 cells per cluster),

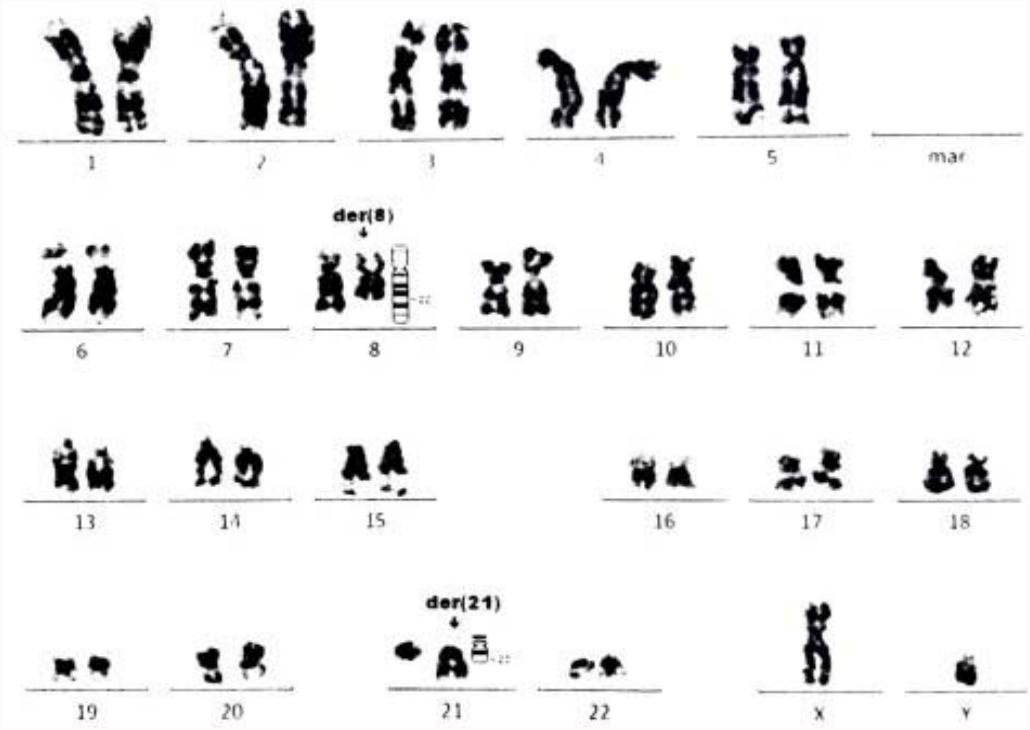

Figure 3: Conventional G-banded cytogenetics performed on bone marrow aspirate sample from the index case showing 46, XY, t (8;21) (q22; q22) in all the metaphases analyzed. Moreover, AML1-ETO (RNUX1-RUNX1T1) fusion transcripts were also detected by reverse transcript-polymerase chain reaction (not shown) consistent with a diagnosis of AML (M2 phenotype).

sheets, and at places paratrabecular and perivascular aggregates pointing to their neoplastic phenotype. The myeloid blasts ranged from 10% to 70% which showed a typical immunophenotypic pattern of expression in most of the cases. On immunophenotyping, the neoplastic mast cells consistently expressed CD117, CD25, variably for CD2, and tryptase whereas CD34, HLA-DR, MPO were negative. On flowcytometry, dim to moderate CD45 positivity *vs.* high side scatter and bright expression of CD117, CD25, and/or CD2 typified neoplastic mast cell population [10].

AML1-ETO (RUNX1/RUNX1T1) fusion transcript and/or t (8; 21) was the most common underlying abnormality reported in 11/15 (73.3%) cases, t (1; 9) in one case [12], and no abnormality in one case of AML [11] which harbored myeloid blasts ranging from 10% to 70% in the BM. The mutation analysis performed on either peripheral blood and/or BM aspirate sample (N=13/15) showed a mutated KIT D816V in 6/13 (46%). The outcome following AML directed chemotherapy in such cases were unfavorable with clinical outcome marred by frequent relapse or residual disease or persistence of clonal mast cells [death in 8/15 (53.3%), overall survival ranging from 2 to 115 months]. Won et al. reported that patients with KIT mutations showed significantly higher relapse and death rates than those who were negative [80.0% (4/5) and 83.3% (5/6)] patients who achieved complete remission, respectively). Overall survival was significantly decreased in patients with KIT mutations than those without (418.3 *vs.* 2376.8 days, p=0.008) [14].

Recent 2022 updates on WHO classification of hematopoietic neoplasms have incorporated two separate entities such as Bone Marrow Mastocytosis (BMM) and Well Differentiated SM (WDSM), the latter may occur in any SM subtypes with heavy infiltration of round to polygonal CD25/CD2 negative mast cells in the BM. CD30 positivity, any mutation involving KIT gene, and basal tryptase level >20 ng/ml are now regarded as minor diagnostic criterion [1,15]. Currently, the use of highly sensitive PCR techniques to identify the KIT D816V mutation in peripheral blood has been incorporated into the algorithm for diagnosis of SM, both in adults and children [5].

To conclude, systemic mastocytosis associated with clonal non mast cell hematopoietic neoplasm is distinctly rare in pediatric population which is more commonly associated with t (8; 21) (q22; q22) AML. Meticulous attention to bone marrow cyto-histomorphology and immunophenotypic features is essential for accurate diagnosis for early and aggressive chemotherapy. Although KITD816V mutation is the hallmark abnormality, negative result does not negate the diagnosis; and the prognostic significance such molecular abnormalities needs to be studied in future larger prospective studies.

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