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Transient abnormal myelopoiesis: A case series and review of the literature

Vandana Baloda [a], Papagudi G. Subramanian [a,*], Yajamanam Badrinath [a], Ashok Kumar [a], Pratibha S. Kadam Amare [b], Shripad D. Banavali [c], Brijesh Arora [c], Sumeet Gujral [a]

[a] Hematopathology Laboratory, Tata Memorial Hospital, HBNI, Mumbai, India
[b] Cancer Cytogenetics Division, Tata Memorial Hospital, HBNI, Mumbai, India
[c] Department of Medical and Pediatric Oncology, Tata Memorial Hospital, HBNI, Mumbai, India

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ABSTRACT

Transient abnormal myelopoiesis (TAM) is a rare and unique disorder affecting Down syndrome (DS) newborns. This case series presents 5 cases of Down syndrome with TAM diagnosed during 2007–2015 with detailed analysis of immunophenotypic data of each case. CD34, CD13, CD33, CD117, CD41, CD61, CD7 and HLA-DR are useful markers for characterization of blasts of TAM.

1. Introduction

Children with Down syndrome have an increased risk of acute leukemia (10–100 fold) compared to non-Down syndrome children [1,2]. Two forms of megakaryocytic leukemia namely transient abnormal myelopoiesis (TAM) and acute megakaryoblastic leukemia (AMKL) are seen frequently in Down syndrome children [3].

TAM affects 4–10% of neonates with Down syndrome [3–6]. TAM is a unique entity with its universal linkage to trisomy 21, occurrence limited to the fetal and neonatal life which resolves spontaneously over a period of several weeks to 3 months [6,7]. However in 20–30% of TAM patients, acute megakaryoblastic leukemia subsequently develops in 1–3 years [6,8,9].

2. Materials and method

Tata Memorial hospital database was searched for cases from 2007 to 2015. There were a total 6898 cases of acute leukemia. Of the 45 cases of infantile leukemia, 5 cases of TAM were found.

Five DS patients with TAM who presented to the department of hematopathology, Tata Memorial Hospital, Mumbai between 2007 and 2015 were evaluated retrospectively. The collected data include age, sex, clinical features, cytogenetic and hematological findings including immunophenotypic details. Flow cytometry was performed on peripheral blood or bone marrow specimens using 6–8 color antibody panel against a variety of myeloid, megakaryocytic, erythroid, monocytic and lymphoid markers. For Immunophenotyping sample was prepared by ammonium chloride lysis followed by antibody staining with appropriate volume of pretitrated antibodies. At least 10,000 cell events were acquired and analyzed on BD FACS Canto II (BD Biosciences).

3. Results

Of the five cases of Down syndrome children 3 were males and 2 were females. The age at diagnosis ranged from 5 to 45 days. The children presented with fever, organomegaly and failure to thrive. Dysmorphic features associated with Down syndrome were seen in all children. Hematological findings included high white blood cell counts and high percentages of blasts in peripheral blood and/or bone marrow. Blasts were medium to large in size with agranular basophilic cytoplasm (Fig. 1). Blasts showed cytoplasmic blebs in 3/5 cases. Auer rods were absent. The blasts were cytochemical MPO

* Corresponding author. Hematopathology Laboratory, 7th Floor, Annex Building, Tata Memorial Centre, Dr E Borges Road, Parel, Mumbai, 400 012, Maharashtra, India.
E-mail address: pgs_mani@yahoo.com (P.G. Subramanian).
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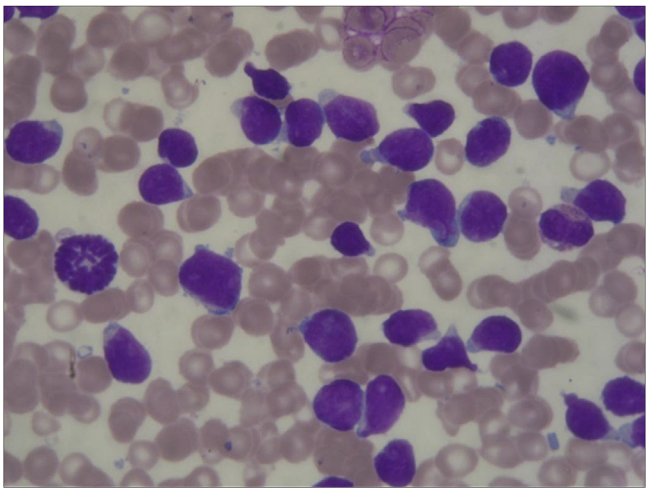

Fig. 1. Photomicrograph Large blasts with basophilic agranular cytoplasm.

negative in all cases. Table 1 depicts the age, sex and immunophenotypic parameters of each case.

Immunophenotypic analysis using multi-color flow cytometry revealed that the blasts in all cases expressed stem cell marker CD34 and myeloid marker CD33. Majority cases (4/5) expressed c-kit (CD117) (Figs. 2 and 3). Expression of megakaryocytic markers CD41 and CD61 (Fig. 4), aberrant expression of T − lineage associated marker CD7 and CD56 expression was also noted (Fig. 5).

Cytogenetic studies in all cases showed a karyotype of 47 XY, +21. There was no evidence of MLL translocation, t (1; 22), monosomy 7/del 7q, monosomy 5/del 5q or trisomy 8. A repeat complete blood count in one case revealed a decreasing trend in the total leucocyte count and percentage of blasts. Two of the babies died in the newborn period due to sepsis.

4. Discussion

Bernhard et al. first in 1951 described a TAM case which was listed among cases of congenital leukemia [10]. Later in 1954, Schunk and Lehman identified that TAM is limited to Down syndrome [11]. Trisomy 21 is linked to the disease pathogenesis is evident by the fact that even children who are mosaic for trisomy 21 but phenotypically normal share the increased risk of developing TAM and subsequent leukemia [7,17]. However, TAM can occur in phenotypically normal neonate and in these cases infants are either mosaic for trisomy 21 or have an acquired trisomy restricted to leukemic clone [17]. Later it was recognized that there is a risk of subsequent leukemia of megakaryocytic lineage in TMD survivors [12,13].

4.1. Molecular pathogenesis

In 2002 Wechsler et al. demonstrated that X-linked GATA1 gene mutations are solely associated with Down syndrome AMKL [14]. It was shortly followed by the discovery that GATA1 is the leukemogenic mutation in TMD described by Hitzler et al. [15] and Mundschau et al. [16]. TAM and DS-AMKL are linked clonal disorders characterized by accumulations of immature megakaryoblasts in peripheral blood and/or liver. Two distinct genetic events implicated in the pathogenesis of TAM are Trisomy 21 and somatic mutations of X-linked GATA1 gene. In the absence of trisomy 21, GATA1 mutations cause a different phenotype of anemia and neutropenia and not leukemia [18]. TAM has not been reported to occur outside the presence of trisomy 21.

Somatic mutations of GATA1 gene are pathognomonic for all myeloid leukemia in Down syndrome children i.e. TAM and AMKL [14–16,21]. GATA1 gene is located on X-chromosome and encodes for a zinc finger transcription factor that is plays an important role in normal erythropoiesis and megakaryopoiesis. It is a negative regulator of megakaryocytic proliferation and facilitates megakaryocytic maturation. A full length 50 KDa GATA1 protein regulate the differentiation and proliferation of megakaryocytes. A wide variety of mutations, including missense, deletions, insertions, majority involving exon 2, and less commonly exon 3, ultimately yields a truncated or shortened 40 KDa protein GATA1s. This isoform lacks the N-terminal transactivation domain but retains both Zn fingers involved in DNA binding as well as interaction with its co-factors, friend of GATA1 (FOG1). This leads to uncoupling of megakaryocytic differentiation and proliferation and abnormal megakaryopoiesis in TAM [22].

TAM is a disorder of fetal hematopoiesis [5,19,20]. The fetal liver Hematopoietic Stem Cell/progenitor cell develops the disease in utero which is supported by the fact that majority of TAM resolves spontaneously as with few months of birth hematopoiesis in fetal liver ceases and fully switches to bone marrow. Also in cases of severe TAM cases there is massive hepatic fibrosis because of megakaryocytic infiltration with relative sparing the bone marrow

Table 1
Immunophenotypic and demographic profile of patients.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age at presentation	5 days	45 days	11 days	Neonate	40 days
Sex	M	M	F	F	M
Cytogenetics	Trisomy 21	Trisomy 21	Trisomy 21	Trisomy 21	Trisomy 21
Blast %	80 (BM)	57(BM)	77 (PB)	59(PB)	20(PB)
MPO	–	–	–	–	–
CD 34	+	+	+	+	+
CD 13	–	–	+	–	–
CD 33	+	+	+	+	+
CD 117	+	+	+	–	+
Anti MPO	ND	–	+	ND	–
CD 41	+	–	+	WK +	Inconclusive
CD 61	+	–	+	WK +	Inconclusive
CD 14	–	ND	–	ND	ND
CD 235a	–	–	ND	ND	ND
CD 7	–	+	+	–	+
CD 56	+	–	+	–	–
HLA DR	–	+	–	–	–

Abbreviations: M, male; F, female; +, positive; -, negative; ND, not done; WK+, weak positive; BM, bone marrow; PB, Peripheral blood.

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