Case Report

A rare case of acute myeloid leukemia in a 4-day-old neonate with concurrent trisomy 21 and trisomy 18

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ABSTRACT

Neonates with trisomy 21 often present with hemato-lymphoid neoplasms, especially in the first 5 years of their life. In such neonates, acute myeloid leukemia, if at all occurs, is preceded by a preleukemic condition known as transient abnormal myelopoiesis (TAM), comprising blast proliferation, which is often self-limiting and rarely may progress into a full-blown case of acute leukemia. We report a case of a neonate with suspected acute leukemia, referred from a Government Medical College for immunophenotyping by flow cytometry, which we reported as acute leukemia along with a possibility of TAM. As karyotyping was not feasible due to sample degradation, however, fluorescence *in situ* hybridization was performed as a part of further work-up, which surprisingly detected both trisomy 21 and trisomy 18. Unfortunately, the neonate succumbed to respiratory distress and cardiac arrest on day 7, before initiation of therapy. The simultaneous occurrence of trisomy 21 and trisomy 18 in a neonate with suspected hemato-lymphoid malignancy is a rare and noteworthy cytogenetic anomaly. This case underscores the critical role of flow cytometry and molecular diagnostics in neonatal leukemia evaluation.

Key words: Acute leukemia, Dual trisomy, Neonate, Transient abnormal myelopoiesis

Down syndrome (DS) or trisomy 21 is a chromosomal disorder accompanied by numerous anomalies, one of which includes abnormal leukemogenesis. Even though the occurrence of transient abnormal myelopoiesis (TAM) and/or acute myeloid leukemia (AML) has been reported, and a lot has already been journaled on it in the past. However, this case is an extremely rare presentation of co-occurrence of trisomy 21 having a flowcytometry confirmed hematolymphoid malignancy with trisomy 18, which is a serious genetic condition involving severe developmental issues. For trisomy 21, the syndrome predisposes to a range of hematopoietic disorders broadly including AML and acute lymphoblastic leukemia (ALL) [1]. Children with trisomy 21 have 50-fold increased risk when compared with the general pediatric population of developing acute leukemia [2]. In case of AML, the abnormality in hematopoiesis develops in utero itself, also known as myeloid leukemia (ML) of DS [3,4]. This abnormal myelopoiesis is not clinically apparent in about ~80% cases and usually resolves by itself within a few months after birth [1,3]. This self-limiting disorder has been named as TAM and is characteristically considered a pre-leukemic condition. The abnormal proliferation of blasts in TAM has the potential to convert into a full-blown picture of acute leukemia of megakaryoblastic lineage. This has been observed in approximately in ~10% of such infants. In the remaining 80–90% infants, this plays as a clinically silent condition which resolves itself spontaneously within a few months after birth and is apparent through a decreasing trend in total leukocyte counts in serial complete blood counts (CBCs) [5]. The root cause of this abnormal leukemogenesis or TAM-DS is caused by mutations in n-terminal region of transcription factor GATA1 [6-11]. Considering its transient nature TAM follows a benign course; however, in about 20–25% cases, TAM will have chance to develop into a full blown picture of AML requiring disease specific treatment and can occur any time before 5 years of age or early childhood. This transformation occurs with the addition of secondary mutations over the GATA 1 mutation, supporting the persistence of this abnormal clone in TAM [12]. For trisomy 21-associated acute leukemia, whether it is AML or ALL, both present with comparable clinical behavior, prognosis, and response to treatment, which is slightly better in AML and achieves long-term survival post-treatment as compared to ALL, where it is inferior and follows a more aggressive approach. However, in the case of relapse, both give poor outcomes.

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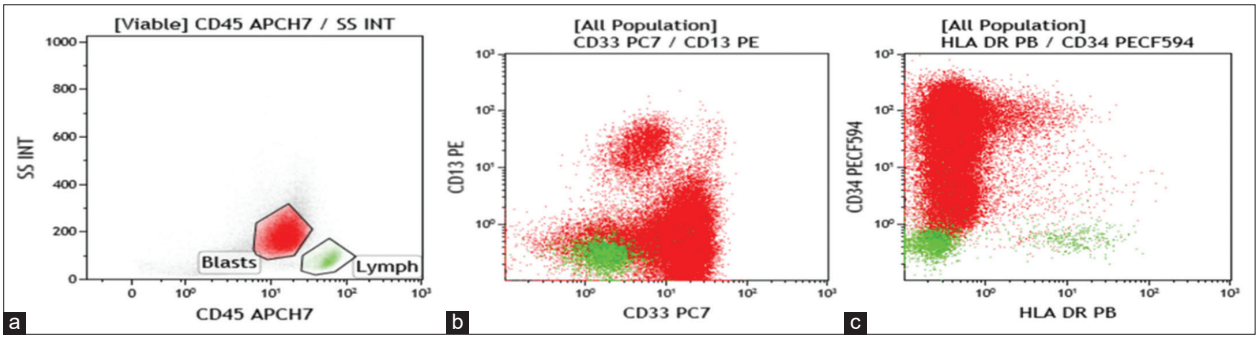

Figure 1: Dot plot showing (a) CD45 dim positive blast population (red); (b) Blasts (red) showing CD13 and CD33 positivity; (c) Blasts (red) showing CD34 positivity

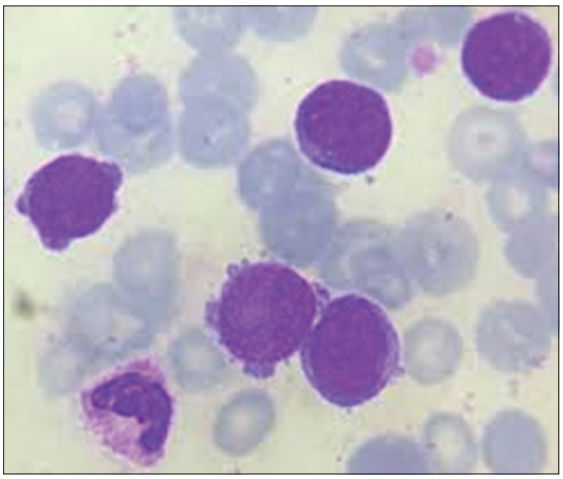

Figure 2: MGG stained smears show blasts showing high N:C ratio and cytoplasmic blebs (indicating megakaryoblastic morphology) (X100)

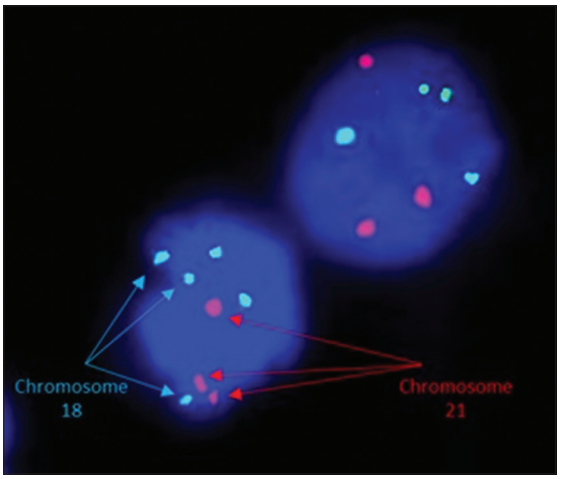

Figure 3: There is trisomy 18 found in 30% of the cells in addition to primary cell line consistent with trisomy 21. The red, aqua, and green signals show chromosome 21, 18, and 13, respectively. The interphase cells are counterstained with DAPI II (blue)

Even though TAM-DS and AML-DS are well-documented entities, the coexistence of the same with trisomy 18 is a rare scenario. Not much has been reported on these coexisting trisomies, making it a case of special interest to consider and understand. Trisomy 18 is also a chromosomal disorder, also known as Edward syndrome, and imposes a variety of physical and developmental abnormalities. Most individuals with trisomy 18 die before birth or shortly after birth, and those who manage to survive are the ones with severe physical and intellectual disabilities.

CASE REPORT

We report a case of a neonate whose heparinized bone marrow aspirate sample was received for immunophenotyping due to suspicion of acute leukemia reported in a hemogram at a government medical college in India. The sample was analyzed for immunophenotyping by flow cytometry at Pathkind-National Reference Lab in the section of specialized hematology.

The sample was processed using the wash-stain-lyse method and later analyzed by BC Navios flow cytometer by Beckman Coulter, which is a 3-laser, 10-color platform. For immunophenotyping, we used our pre-defined acute leukemia panel comprising of the following markers: CD45, myeloperoxidase (MPO), CD117, CD19, CD20, CD10, CD38, CD34, CD13, CD33, CD14, CD64, CD41, CD61, and human leukocyte antigen-DR (HLA-DR).

Dot plots revealed a CD45 dim positive blast population showing positivity for CD34, CD117, CD13, CD33, CD64, CD41, CD38, and HLA-DR. Negative markers included CD19, MPO, CD10, CD20, CD14, and CD61 (Fig. 1). Based on this immunophenotype, we reported the case as AML, megakaryoblastic subtype, considering positivity for CD41, which is a known marker for megakaryoblast lineage. Considering an apparent positivity of CD117, CD34, CD41, and negative expression of MPO along with B lineage markers, we suggested a possibility to consider the occurrence of TAM-DS, making karyotyping and monitoring through serial CBCs a necessary part of the further work-up plan.

Due to partial sample deterioration (3 days old) and requirement for viable cell culture, conventional karyotyping could not be performed. Considering the precious nature of the sample and the desire to follow-up the case, we instead sent the sample to the molecular department of the reference lab to perform FISH, which interestingly revealed the presence of dual chromosomal abnormalities, that is, trisomy 21 along with trisomy 18 (Figs. 2 and 3).

On further need to know about the clinical condition of this case, the concerned clinician was referred, and we were informed about the tragic death of the neonate on day 7, the cause of death being respiratory distress and

cardiac arrest, which happened before initiation of any disease-specific therapy.

DISCUSSION

Co-occurrence of dual chromosomal anomalies is a rare circumstance. Trisomy 21, also called DS and trisomy 18, also called Edward syndrome, are two different chromosomal disorders presenting with different clinical predispositions. Trisomy 21 is commonly associated with predisposition to hematological malignancies, one of which is AML-DS [13]. The initial presentation may be confusing, as out of these ~80% cases present with clinically silent disease, which may resolve spontaneously after 3–4 months [14]. Due to its transient nature, the entity is called TAM. It is only after its known status of trisomy 21 accompanied by GATA 1 mutation and follow-up with serial CBCs showing a decreasing trend of total leukocyte count, that we can confirm the diagnosis of TAM [15]. Furthermore, it further necessitates the need to monitor for a period of the initial 5 years as the disease has a potential for remission, which is maximum during this early childhood. It is when the cell clone with GATA1 mutation persists, which later acquires secondary mutations, leading to conversion to an overt AML-DS. Few studies done on prenatal and cord blood samples from babies with DS have shown that somatic GATA 1 mutations are acquired before birth, most likely during the second trimester. This points to disease being borne *in utero* itself, which later presents either as TAM or may convert into a more aggressive form, that is, AML. Interestingly, in all cases of AML-DS, one common finding noted was the blasts expressed megakaryoblastic markers along with negative expression of MPO. In our case, blasts showed positivity of one of the meagakaryoblastic markers which were CD41, diagnosis being also supported by negative expression of MPO.

Trisomy 18 is a chromosomal disorder of rare occurrence and is more aggressive in clinical approach in comparison to DS. It is noteworthy to mention its association with multiple congenital anomalies, severe intellectual disabilities, and high morbidity. Most individuals with this trisomy are unable to survive beyond the neonatal period. Its clinical picture is severe and diverse, thereby involving various organ systems. Given the typically poor prognosis associated with Edwards's syndrome, the neonatal demise on the 6th day post-birth in our case, involving a neonate with trisomy 18, aligns with the expected clinical course of this chromosomal disorder. Had it been otherwise, with a neonate harboring isolated trisomy 21, the child might have survived with its associated clinical implications and predisposition to TAM or ML-DS. Unfortunately, in this case, the neonate was found to have dual trisomies, that is, 21 and 18, which led to his tragic death in the 1st week of life.

While there is no specific treatment or therapeutic approach to Edward syndrome and DS; however, early diagnosis might be of help in appropriate management and also might point to the need for parental counseling well in time.

CONCLUSION

Considering this rare scenario of co-occurring trisomies, it makes the diagnosis and pathogenesis more complex, thereby posing a challenge in providing a definitive and timely treatment. It, therefore, prompts an investigation of further insights into the pathogenesis of a hematolymphoid malignancy in association with dual chromosomal abnormalities.

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