Case Report

Down syndrome presenting with different hematological manifestations: A case series of four cases

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Abstract

Children with Down syndrome (DS) are found to have an increased risk of developing various hematological disorders. Particularly, they have an increased predisposition to acute leukemia, predominantly the myeloid type known as myeloid leukemia of Down syndrome (ML-DS). The major morphological subtype is acute megakaryoblastic leukemia. Approximately 10% of the neonates with DS show a unique disorder known as transient leukemia or transient abnormal myelopoiesis (TAM). Their clinical and morphological features are indistinguishable from acute myeloid leukemia (AML); however, they regress spontaneously within the first few months of life. Here we present a series of four cases with different hematological conditions in children with DS. Of the four cases, two presented with AML-M7, one with TAM, and one case was diagnosed as AML-M2 subtype. This case series highlights the spectrum of hematological disorders in children with DS. Although the majority of the case studies show that TAM and AML-M7 are strongly associated with DS, this case series brings to focus that other AML subtypes may occur as well.

Keyword: Acute leukemia, Down syndrome, megakaryoblast

Introduction

Krivit and Good first described the association between Down syndrome (DS) and leukemia in 1957.[1] Children with DS present with a wide spectrum of hematolymphoid disorders ranging from transient abnormal myelopoiesis (TAM) that resolves spontaneously to frank acute leukemia of both myeloid and lymphoid lineages.[2] There is a 10-20-fold increased risk of acute leukemia in these patients with a 46- to 83-fold increased incidence of acute myeloid leukemia (AML) and a 10- to 27-fold increased risk of acute lymphoblastic leukemia.[3] Among the myeloid lineage, the acute megakaryoblastic leukemia (AMKL/AML-M7) subtype predominates in the first 4 years of life.[4] There is a paucity of data reported from India regarding the hematological disorders in children with DS. Surprisingly, in a span of 2 years, we received a total of four cases of pediatric patients with DS presenting with varied hematological abnormalities

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Received: 29-02-2020 **Revised:** 27-03-2020
Accepted: 15-04-2020 **Published:** 31-05-2020

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_326_20

Case 1

A 4-week-old male child with features of DS presented with fever and petechiae of 5 days' duration. Conventional karyotyping confirmed the diagnosis of DS. Physical examination revealed severe pallor and moderate hepatosplenomegaly. Laboratory investigations revealed a high total leukocyte count (TLC) of 25,000/Cumm, Hb of 6.3 gm/dL and a low platelet count of 60,000/Cumm. Peripheral blood smear (PBS) and bone marrow aspiration (BMA) smears revealed blast accounting for 50%.

How to cite this article: Shangpliang D, Dey B, Das J, Baishya P, Raphael V, Khonglah Y. Down syndrome presenting with different hematological manifestations: A case series of four cases. J Family Med Prim Care 2020;9:2569-72.

These blast cells have high an N: C ratio, round to irregular nuclei, moderate basophilic cytoplasm with occasional cells showing cytoplasmic blebs [Figure 1a]. On cytochemistry, these blasts were negative for myeloperoxidase (MPO) and Sudan Black B (SBB). Immunophenotyping revealed markers positive for CD41, CD61, CD13, and CD33 antigens, and negative for CD3, CD4, CD8, CD20, CD10, and HLA-DR [Figure 1b]. A diagnosis of AML-M7/AMKL was made. The patient's condition deteriorated rapidly and was put on supportive treatment. The patient died within 1 week of admission.

Case 2

A 1-year-old male child presented with fever and progressive weakness of 10 days' duration. Physical examination revealed severe pallor and mild hepatosplenomegaly and features of DS. Complete blood count revealed Hb of 5.4 gm/dL, leukocytosis with a TLC of 63,000/Cumm and platelet count of 15,000/Cumm. Differential count on PBS showed 78% blasts, 15% neutrophils, 4% lymphocytes, and 3% eosinophils. BMA showed 85% blasts. These blasts were heterogenous and many showed cytoplasmic blebbing reminiscent of megakaryoblast [Figure 2a and b]. These blasts were negative for MPO and SBB. Immunophenotyping by flow cytometry revealed the blasts were positive for CD41, CD61, CD33, and HLA-DR antigens, and were negative for CD3, CD4, CD8, CD10, and CD20. The final diagnosis of AML-M7 was made. Chemotherapy was started with low dose cytarabine; however, the condition of the baby deteriorated. The coagulation profile was deranged with raised prothrombin time suggestive of disseminated intravascular coagulation (DIC). The patient expired after 4 months of hospital stay.

Case 3

A 2.2-kg female baby was born at term to a 38-year-old lady by normal vaginal delivery. There was a history of respiratory distress and the baby was admitted to the neonatal intensive care unit. On physical examination baby was noticed to have anti-mongoloid slant, low set ears, short neck, short stubby fingers, and hypotonia. Conventional karyotyping confirmed the diagnosis of DS. A routine hemogram showed that the TLC was 28×10^3, Hb was 10.7 gm/dL and platelet count was 1 lakh/Cumm. The PBS showed 22% blasts, 5% promyelocyte, 15% myelocyte, 54% neutrophils, 1% eosinophil, and 3% basophils. The blasts were medium to large size with round nuclei, fine nuclear chromatin, and basophilic cytoplasm. Some of the blast cells showed cytoplasmic blebs or projections. On cytochemical stains, these blasts were negative for MPO and SBB. BMA was deferred and the baby was kept under close monitoring with repeat PBS after 2 weeks. The baby was observed and treated symptomatically. In the third week, a repeat complete hemogram showed Hb of 12.5 gm/dL, platelet count of 1.7 Lakhs/Cumm, and the TLC of 11,000/Cumm with a blast count of 2%. Spontaneous remission was observed in 2 months. The final diagnosis of TAM associated with DS was made.

Case 4

A 3-year-old male child with features of DS presented with fever, purpura, and ecchymosis of 6 days' duration. Physical examination revealed pallor with mild hepatosplenomegaly. Routine blood investigation showed a high TLC of 1,29,000/Cumm, Hb of 9.0 gm/dL and a low platelet count of 38,000/Cumm. The differential count on PBS was 65% blast, 20% neutrophil, 7% lymphocyte, 5% monocyte, and 3% eosinophil. The BMA showed myeloid hyperplasia with an increase in blasts comprising 78% of the marrow cells along with myeloid maturation. These blasts were heterogenous and some had granular cytoplasm, though distinct Auer rods were not identified [Figure 3a]. On cytochemistry, the blasts were positive for MPO and SBB, and negative for (Periodic Acid Schiff) PAS stain. Immunophenotyping was performed and the blasts showed a positive reaction for CD13, CD33, CD117, and HLA-DR antigens [Figure 3b]. The blasts were negative reaction for CD3, CD10, CD20, CD4, CD8, CD14, CD41 and CD61. The final diagnosis of AML with maturation (AML-M2) was made. The patient was lost to follow-up.

Discussion

DS due to trisomy 21 is the commonest chromosomal abnormality in a live newborn and occurs approximately 1 in 1000 live birth.[2,3] Among the diverse hematological disorders seen in DS, the development of leukemia is considered to have a 10 to

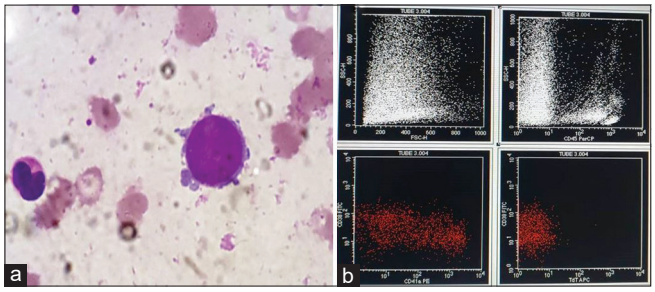

Figure 1: (a) PBS showing blast with high N: C ratio, round to oval nuclei with cytoplasmic blebbing (Leishman stain, 40×). (b) Immunophenotyping by flow cytometry showing heterogenous positivity for CD41 antigen

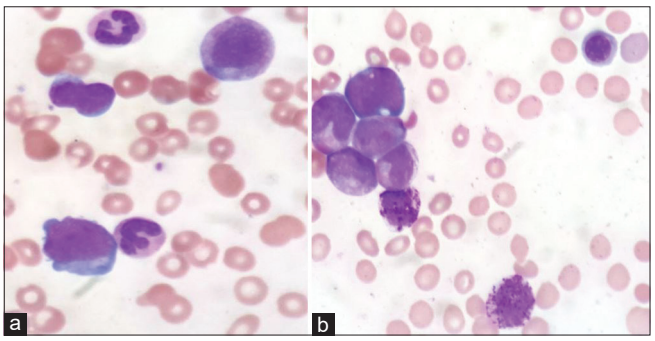

Figure 2: (a) PBS with increased number of myeloblasts with occasional blast showing cytoplasmic blebs. (Leishman stain, 40×). (b) PBS showing myeloblasts along with increased basophils. (Leishman stain, 40×)

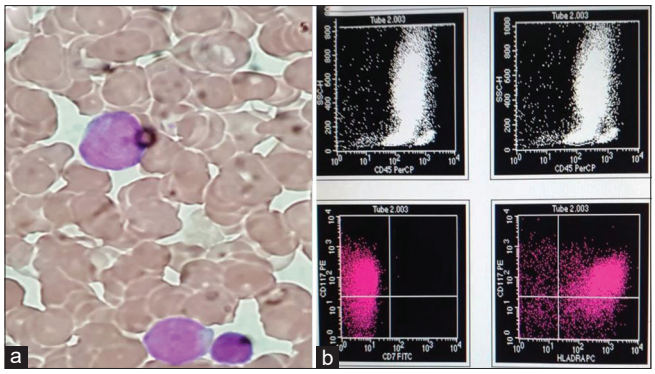

Figure 3: (a) PBS showing varied morphology of myeloblasts (Leishman stain, 40×). (b) Immunophenotyping by flow cytometry showing positivity for CD117 and HLA-DR antigens

20-fold increased incidence.[4] Myeloid proliferation associated with DS has been incorporated as a distinct entity in the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues.[2]

Approximately 10% of the neonates with DS develop a unique hematologic abnormality known as the TAM, characterized by the transient appearance of blast cells in the peripheral blood and usually disappears spontaneously during the first few months of life.[2] Thrombocytopenia is the most common presentation, while other cytopenias are less frequently encountered in TAM. Leukocytosis is present in 30%–50% cases of TAM which includes increased neutrophils, myelocytes, monocytes and basophils.[5] According to the Oxford Imperial Down Syndrome Cohort (OIDSC) study, TAM has been classified as those cases with blasts accounting for >10%. These blast cells are typically described as megakaryoblastic with cytoplasmic blebbing and basophilic cytoplasm and are virtually indistinguishable from the blasts of AMKL.[5,6] On cytochemistry these blast cells show occasional granular positivity for PAS and negative for MPO, SBB, and NSE stains. In our study, case 3 showed blast cells morphologically and cytochemically consistent with megakaryoblast, peripheral blood basophilia with spontaneous remission within 2 months of primary evaluation confirming the diagnosis of TAM associated with DS.

There is an approximately 150-fold increased incidence of AML in children with DS, virtually developing below 5 years of age.[5] ML-DS neonates usually present with lethargy, poor feeding, pallor, purpura, respiratory distress, and hepatosplenomegaly.[3] The vast majority of DS associated AML cases are the AMKL/AML-M7 subtype. As per the FAB classification, AML-M7 is defined by the presence of more than 20% blasts that are megakaryocytic lineage in BMA determined by morphology and immunophenotyping.[7] The PBS, BMA morphology and cytochemical profile of these blast cells are similar to those seen in TAM. In our study, case 1 and case 2 were diagnosed as AML-M7 of DS. Although AML-M7 is considered to be the most common morphological subtype seen in patients with DS, other AML FAB subtypes have also been considered in ML-DS including M0, M1/M2, and M6, less frequently.[8] In our study case 4 has been diagnosed as AML-M2.

Immunophenotyping by using multiparameter flow cytometry has been analyzed by Karandikar *et al.*[9] in TAM and AML in DS patients. Their study suggests that the blast population of AML and TAM in DS share similar characteristics which include a positive reaction for CD45, CD33, CD41, CD61, CD34, and a negative reaction for CD14 and CD64 antigens indicating a megakaryocytic differentiation.[9] A recent study suggests a particular genetic mutation "GATA 1" mutation associated with most patients of DS with TAM and AML. GATA 1 gene is a key regulator of megakaryocyte and erythroid differentiation. This mutation was found to be favorable for these patients as it contributes to greater sensitivity for a specific chemotherapeutic drug such as cytosine arabinoside which leads to its greater survival.[10]

Children with ML-DS have a better outcome compared with children without DS with a long-term survival 74%–91%.[5] Early death, however, occurred in up to 20% of infants and was significantly related with higher white blood cell count at diagnosis, increased liver enzymes and a failure to normalize the blood count.[11]

The incidence of DS increases with maternal age, and its occurrence varies in different populations ranging from 1 in 319 to 1 in 1000 live births.[12] As already discussed, there are several hematological disorders associated with DS including TAM and frank leukemia.[12] Thus, family physicians should be aware of the higher risk of DS associated with increased maternal age as well as the hematological disorders associated with DS.

In spite of significant developments in the diagnostic modalities of DS and leukemia associated with DS, clinical examination and PBS examination remain invaluable components of primary care of these subjects.[13,14]

Conclusion

The present case series highlights the varied spectrum of hematological conditions associated with DS. Although patients with transient leukemia may regress spontaneously, it is warranted that such patients must be kept under regular follow-up for early detection of transformation to acute leukemia. Besides the AMKL being the most common ML-DS, other subtypes such as AML-M2 must also be considered in the diagnosis of leukemia in these patients.

Author contribution

Shangpliang D and Dey B have written the manuscript. Das J and Baishya P have collected and analyzed the data. Raphael V and Khonglah Y have reported the cases. All authors have proofread and edited the manuscript.

Declaration

The manuscript has been read and approved by all the authors. The requirements for authorship as stated above have been met,

and that each author believes that the manuscript represents honest work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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