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Case Report

Pathology Section

Transient Abnormal Myelopoiesis in a Down Syndrome Baby: A Case Report

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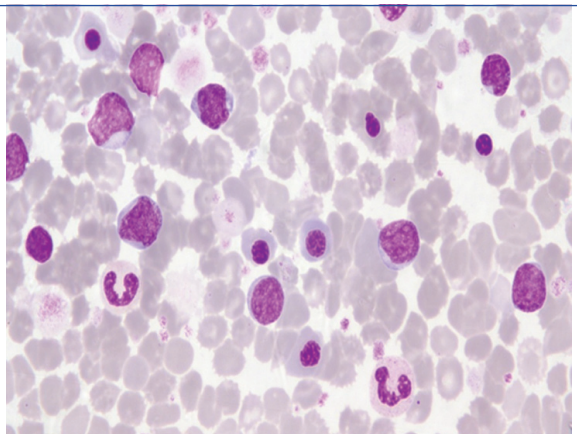
ABSTRACT

Transient Abnormal Myelopoiesis (TAM) is a transient haematological condition observed in children with Down syndrome during their neonatal period. Spontaneous resolution without any specific treatment is the rule, and the condition is known to occur exclusively in association with trisomy 21. Around 10% of Down syndrome babies are known to be affected by TAM, and 20-30% of these babies are known to develop acute myeloid leukaemia, of the megakaryoblastic type, in their later lives. Multisystem involvement is known in this condition. The present case of TAM is a two-day-old newborn female baby, born out of full-term gestation, presented with respiratory distress along with congenital pneumonia, hepatosplenomegaly, and mild ascites. The baby also had significant pulmonary hypertension, an Atrial Septal Defect (ASD), and non restrictive Patent Ductus Arteriosus (PDA). A significant increase in the total leukocyte count was seen, accompanied by thrombocytosis and 72% blastoid cells. Then, using karyotyping, Trisomy 21 was verified. 35% of the blasts had megakaryoblastic differentiation, according to flow cytometry. Hence, before diagnosing congenital leukaemia based on finding excess blasts in the peripheral smear of a newborn, karyotyping has to be done to look for possible trisomy 21. It can be an incidental finding, as in the present case, without prior clinical suspicion of Down syndrome.

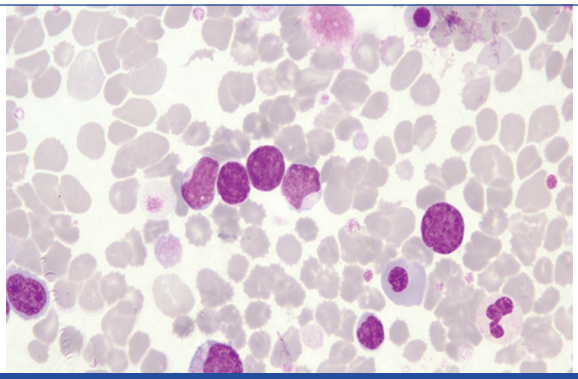
Keywords: Acute megakaryoblastic leukaemia, Congenital leukaemia, Flow cytomery, Karyotyping, Trisomy 21

CASE REPORT

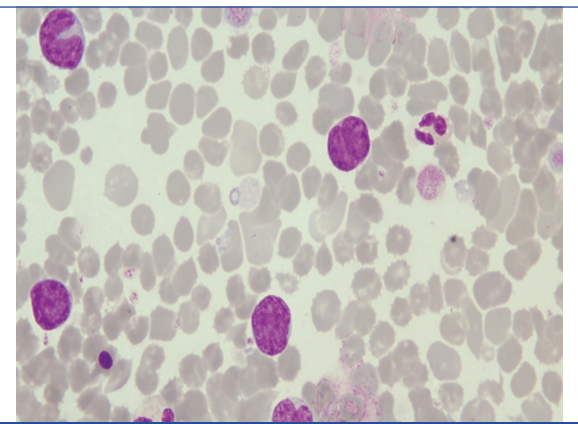
A full-term newborn female, weighing 2.2 kg, was delivered by lower segment caesarean section and admitted to our hospital's neonatal intensive care unit for post-resuscitation care. The results of a general physical examination did not reveal dysmorphism. A chest X-ray revealed a right middle zone patch, suggesting congenital pneumonia, and the baby experienced respiratory distress. There was mild ascites and hepatosplenomegaly. The echocardiography also revealed non restrictive PDA, ASD, and significant pulmonary hypertension. Elevated bilirubin was noticed on the first day itself. Total bilirubin was 11.35 mg/dL (normal range 0-1.2 mg/dL) with conjugated bilirubin being 1.42 mg/dL (normal range 0-0.2 mg/dL) and C-reactive protein was 18.44 mg/L (normal range 0-5) on septic work-up. Coagulation tests were also deranged with Prothrombin time of 81 (normal 11.6-14 seconds) and activated Partial Thromboplastin Time (aPTT) of 110 (normal 24.9-37.9 seconds). The total White Blood Cell (WBC) count was markedly elevated, with a count of 1.2 lac/cumm (normal range 10000-26000 cells/cumm) [Table/Fig-1]. There was thrombocytosis with a platelet count of 5.9 lac/cumm (normal 1.5-4.5 lac/cumm). Haemoglobin was 13 g/dL (normal 14-22 g/dL). The peripheral smear showed 38% nucleated Red Blood Cells (RBCs), and 72% of the WBCs had a blastoid appearance with a high N:C ratio, fine open nuclear chromatin, some having 2-3 prominent nucleoli, and a scant to moderate amount of basophilic cytoplasm [Table/Fig-2]. Platelets were significantly dyspoietic, with many giant and hypogranular forms noticed [Table/Fig-3]. A blood sample was submitted for flow cytometry and karyotyping due to a significant suspicion of



[Table/Fig-1]: Elevated total WBC count displaying blasts with high N:C ratio, lymphocytes, neutrophils, erythroblasts and hypogranular giant platelets. (Leishman stain, 1000x).



[Table/Fig-2]: Peripheral smear showing blasts with a high N:C ratio, fine nuclear chromatin, prominent nucleoli, and scanty basophilic cytoplasm. (Leishman stain, 1000x).



[Table/Fig-3]: Peripheral smear showing many giant and hypogranular platelets along with blasts. (Leishman stain, 1000x).

TAM. Trisomy 21 was detected in karyotyping, and flow cytometry showed 35% blasts with megakaryoblastic differentiation. The blasts expressed CD34, CD38, CD58, CD7 (subset), CD56 (subset), CD4 (dim), CD33 (dim), CD36, and CD117. However, Cytoplasmic CD41, CD61, CD42b, MPO, cytoplasmic CD3, and other markers tested were negative. The final diagnosis was TAM of Down syndrome. Sepsis was the primary focus of treatment. Unfortunately, the baby died during the hospital stay due to complications from sepsis.

DISCUSSION

Haematological abnormalities are known to be frequent in individuals with chromosomal disorders. Down syndrome, one of the most common chromosomal disorders, is often associated with multiple haematological problems, both benign and malignant [1]. Children with Down syndrome are more likely to experience acute leukaemia in later life. Unlike acute leukaemias, TAM is a temporary condition confined to trisomy 21 neonates. It is characterised by blasts with or without leukocytosis, nucleated RBCs, and a variable population of platelets. It generally resolves spontaneously in a few months [2]. However, the significance of TAM is its potential to transform into acute leukaemia, which is referred to as myeloid leukaemia in Down syndrome and is known to occur in 20-30% of cases of Down syndrome [3,4]. Hence, TAM is rightly considered a leukaemic or preleukaemic syndrome. TAM was initially classified as congenital leukaemia when it was first identified in 1951 [1]. Later in 1954, it was noted that TAM is restricted to Down syndrome [1]. Ten percent of newborns with Down syndrome are known to experience it [5]. Present case of TAM was a two-day-old female baby, presented with neonatal sepsis, later confirmed to have trisomy 21 on karyotyping. In the present case, TAM was an incidental finding during the routine laboratory workup for neonatal sepsis in which there was no clinical suspicion of Down syndrome.

TAM is described as a clonal neonatal preleukaemic syndrome whose pathogenesis is universally linked to Down syndrome [4]. The genetic link is demonstrated by the higher risk of TAM and eventual leukaemia in phenotypically normal children with mosaic trisomy 21 [6]. About 20% of cases can progress to irreversible, overt acute myeloid leukaemia within the first four years of life [6]. Trisomy 21 and somatic mutations of the GATA1 gene are the two known genetic pathways attributed to the aetiopathogenesis of TAM. TAM and trisomy 21 are so strongly linked that the mere presence of the GATA1 gene mutation in the absence of trisomy 21 results in macrocytic anaemia and neutropenia but is not sufficient to develop leukaemia [7]. GATA1 is an important transcriptional regulator of normal megakaryocytic differentiation. It acts as a negative regulator of megakaryocytic proliferation and facilitates megakaryocytic maturation. Leukaemic cells typically exhibit somatic mutations in the gene encoding GATA1. Various mutations in GATA1 can lead to the uncoupling of megakaryocytic differentiation and proliferation, leading to abnormal megakaryopoiesis in TAM [8]. Not all cases of TAM are clinically conspicuous, but most cases manifest in the first two months of life. It can result in intrauterine death or hydrops foetalis in foetal stages [9]. Varied manifestations in a clinically overt disease indicate multisystem involvement of the condition. This is attributed to the infiltration of myeloblasts into various organs such as the liver, heart, bone marrow, pancreas, and skin [10].

The transient nature of the condition is said to be due to the switch over of haematopoiesis from the liver to bone marrow within months after birth [4]. Blasts in the peripheral blood are the clinching point for the diagnosis. The World Health Organisation (WHO) defines TAM as “increased peripheral blood blast cells in a neonate with Down syndrome” without specifying the minimal percentage of blasts [11]. Classically, the cells are large, with basophilic cytoplasm, coarse granules, and cytoplasmic blebs. Immunophenotyping of a TAM blast shows positivity for CD34, CD117, CD13, CD33, CD41, CD42, CD36, CD61, CD7, and CD4 dim, and negative for MPO, CD15, CD14, and glycophorin A [12,13]. Apart from these, moderate leukocytosis is often observed. Haemoglobin levels and platelet counts are variable. A high WBC count of 1.2 lac with 72% blasts was a critical alert in present case to rule out congenital leukaemia. Elevated platelet count, their abnormal morphology, in conjunction with blasts raised suspicion of TAM, resulting in flow cytometric and karyotypic evaluation of the baby’s blood sample for trisomy 21. Hepatosplenomegaly, jaundice, hepatic fibrosis, pericardial effusion, ascites, respiratory distress, and bleeding diathesis are the other rare manifestations of TAM cases [4,10]. However, trisomy 21 itself is inherently known to be associated with multisystem involvement [14]. Respiratory distress and right mid-zone pneumonia were the presenting manifestations in present case. However, hepatosplenomegaly, mild ascites, non restrictive PDA, ASD, and severe pulmonary hypertension were also present. Supportive care is the recommended line of action, and spontaneous remission is the natural outcome in most patients. Rarely, other modalities such as exchange transfusion, leukapheresis, and chemotherapy might be required to reduce the blast population. The overall mortality rate is around 16-23% [4]. Hyperleukocytosis, hepatomegaly with deranged liver function, prematurity, coagulopathy, and failure to normalise the blood counts are considered a few of the factors responsible for early death [9]. The treatment in present case was mainly directed towards sepsis, hyperbilirubinaemia, and deranged coagulation. However, the baby succumbed during the hospital stay due to complications of sepsis. Various cases of TAM are documented in the literature. Falasco BF et al., reported a newborn with Down syndrome, TAM, and basophilic/eosinophilic pericardial effusion without any increase in these cells in the peripheral blood and devoid of any evidence of hypothyroidism [15]. Mishra P et al., documented an interesting case of a neonate with Down syndrome, presented with anaemia, thrombocytopenia, and 75% blasts and was complicated by severe pneumonia [2]. Silvio F et al., reported a peculiar case of TAM in Noonan’s syndrome [16].

CONCLUSION(S)

TAM is unique to Down syndrome. Even in the absence of typical morphological features of Down syndrome, it will be the most likely diagnosis in newborns with an elevated WBC count and blasts in peripheral blood, especially with a normal or high platelet count and abnormal platelet morphology. A high index of suspicion helps to confirm trisomy 21 by karyotyping.

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