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Transient Abnormal Myelosis

[1]Surabhi Mishra, [2]Prakrati Gupta, [3]SudhaIyengar
[1]Post-graduatestudent, [2]Demonstrator, [3]Professor
Department of Pathology, Gajraraja Medical College, Gwalior M.P.

Abstract
Children with constitutional trisomy 21(Down Syndrome, DS)have a unique predisposition to develop myeloid Leukemia of Down syndrome (ML-DS).This disorder is preceded by a transient neonatal preleukemia syndrome, Transient Abnormal Myelopoisis(TAM).TAM andML-DS are caused byco-operation between trisomy-21, which itself perturbs fetal haematopoiesis and acquired mutation in the key haematopoietic transcription factor gene GATA1.These mutations are found in almost one third of DS neonates and are frequently clinically and haematologically "silent." While the majority of cases of TAM undergo spontaneous remission, around 10% will progress to ML-DS by acquiring in the unique biological, cytogenetic, and molecular characteristic of TAM and ML-DS are reviewed here.

Keywords*: Transient Abnormal Myelopoisis, Down Syndrome, Acute Leukemia,Myeloproliferative Disorder.*

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I. Introduction

Transient abnormal myelosis (TAM), also known as transient leukemia or transient myeloproliferative disorder, occurs in approximately 5-10 % of neonates with Down Syndrome(DS)[1,2]Death due to TAM is around 15-23% because of liver and multiorgan failure[3,4].

Approximately 20% of patients subsequently develop acute myeloid leukemia associated with down syndrome (ML-DS) within first 4 years of life.[5]Progression to ML-DS is thought to be due to epigenetic dysregulation found out in DNA methylation study[6].

ML-DS is characterized by the transient appearance of blast cells with megakaryoblastic and/or erythroblastic characteristics in the peripheral blood[7,8]. Approximately 20% of TAM cases result in early death and 16–23% of survivors develop acute megakaryoblasticleukemia (AMKL) within 4 years[9-12].A somatic GATA1 gene mutation is shared by both TAM [13]and AMKL cells[14,15]

Preceding studies have identified several risk factors associated with early death, including high white blood cell (WBC) count (≥100 × 10^9 /L), preterm delivery(<37 weeks), elevated direct bilirubin (>5 mg/dl), hepatomegaly, ascites and bleeding diasthasis[9-12]

ML-DS has a distinct natural history and clinical and biological feature[16,17]

Around 10–15 % of neonates with Down syndrome have a diagnosis of TAM with blasts >10 % and typical clinical features that require close monitoring in the neonatal period since the mortality rate may be up to 20 %. A further 10–15 % of neonates with Down syndrome have one or more acquired GATA1 mutations in association with a low number of circulating blast cells (<10%) and have clinically and hematologically silent disease (Silent TAM)[18]In the majority of cases of TAM and silent TAM, the GATA1 mutant clone goes into complete and permanent remission without the need for chemotherapy. However, 10–20 % of neonates with TAM and silent TAM subsequently develop ML-DS in the first 5 years of life when persistent GATA1 mutant cells acquire additional oncogenic mutations, most often in cohesin or epigenestic regulator genes[19,20]

II. Case Presentation

A premature(32 weeks gestation) and underweight (2.4 kg) 3days old female born to a 24 year old mother by normal vaginal delivery, presented with symptoms of fever and respiratory distress and was admitted to neonatal intensive care unit. The baby was underweight and showed morphological features ofDS, including epicanthic fold and webbed neck.(Figure 1a and b)

Figure 1a: Baby with webbed neck

Figure 1b: Baby with down facies

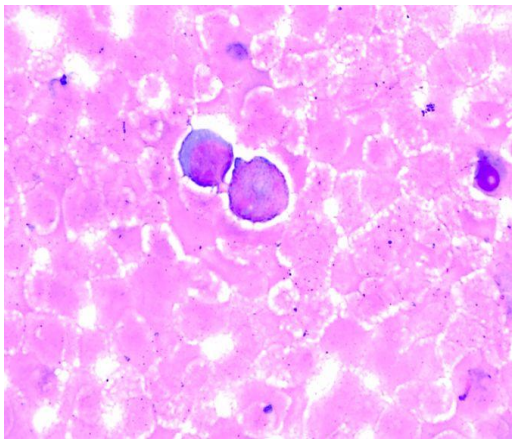

Figure 2a: Blasts

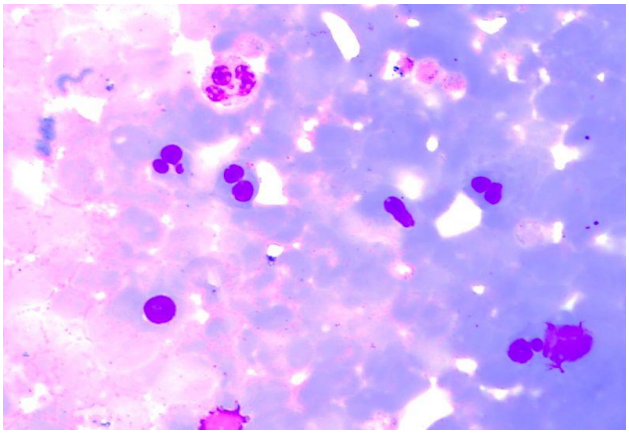

Figure 2b: Dyserythropoisis

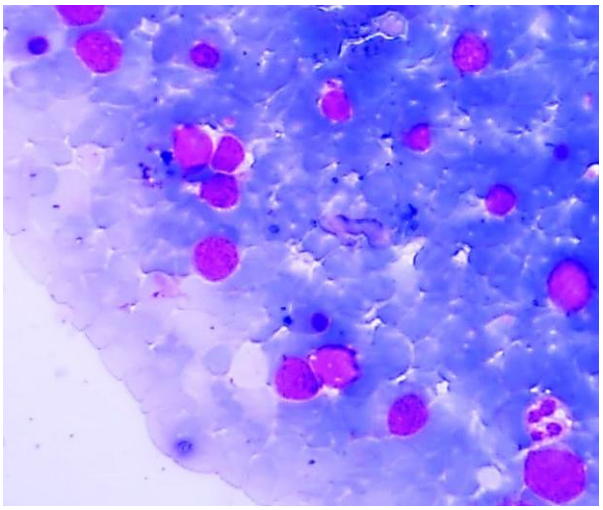

Figure 2c: Hypogranular Giant Platelets

Complete blood Complete blood count (CBC), blood culture, urine culture, LFT, RFT were done.Peripheral smear showed prominent erythroblastemia(112nRBC100 WBC) thus corrected TLC was 32,000/mm^3.Leukocytes comprised chiefly of blasts around50% of intermediate to large size, high N: C ratio, opened up chromatin, 2to 3 conspicuous nucleoli, cytoplasmic bleb and occasional coarse basophilic granulation. (Fig 2a)Myeloid cells showed mild left shift and dysplastic features like hypo granulation.(Fig 2b).Basophilia and eosinophilia was also noted. Thrombocytopenia with giant hypo granular platelets

wereseen(Fig 2c).Red blood cells shows mixed population of microcytic hypochromic to normocytic normochromic cells. In view of suspected clinical features of Down syndrome, CBCand peripheral smear, provisional diagnosis of Transient Abnormal Myelopoisis/Myeloid leukemia associated with Down syndrome was suggested.Bone marrow examination was deferred upon the deteriorating condition of the baby. Flowcytometric immunophenotyping of peripheral blood showed CD 45 dim blasts positive for CD34, CD117, CD13, HLA DR and CD7. They were negative for CD 33, MPO, and T and B cell markers.

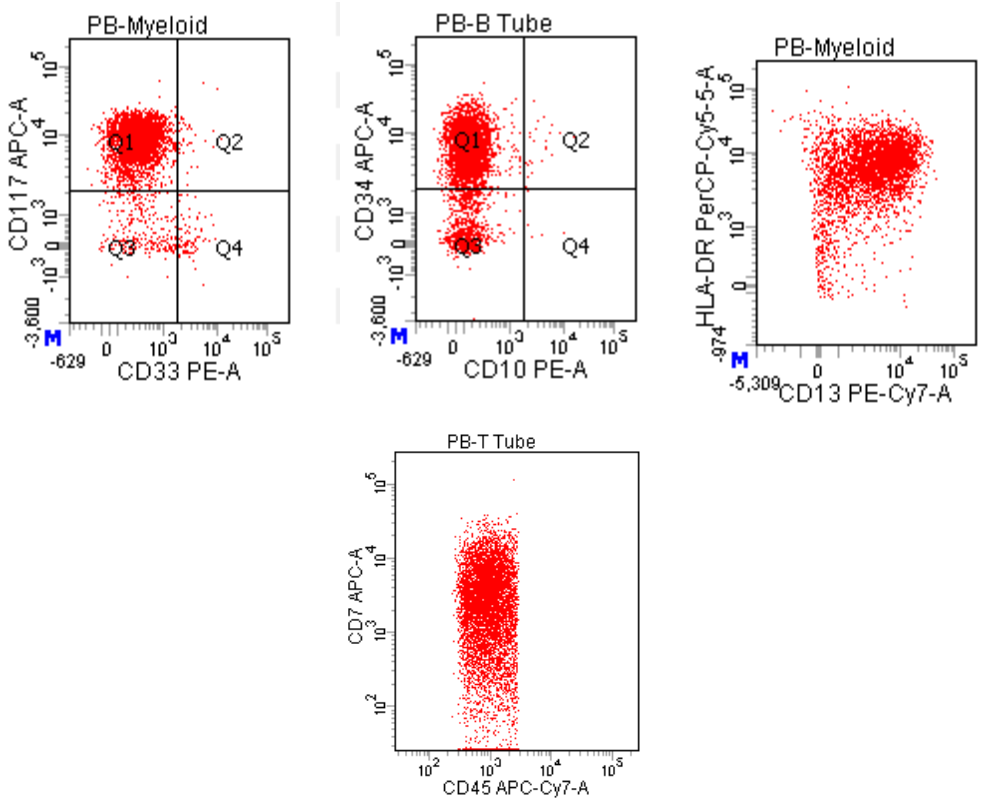

Figure 3: Flowcytometry analysis

Subsequent CBC and peripheral examination showed decrease in WBC count, n-RBC and normalisation of WBC differential. However, baby didn't survive due to multiorgan failure and passed away at the age of 1.5 months.

III. Discussion

Bernhard et al first in 1951 described a TAM case which was listed among cases of congenital leukemia[21]. Molecular Pathogenesis In 2002 Wechsler et al demonstrated that X- linked GATA1 gene mutations are solely associated with Down syndrome AMKL[22].It was shortly followed by the discovery that GATA1 is the leukemogenic mutation in TMD described by Hitzler et al [23].

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[24]. An inherited mutation leading to production of only the short isoform of GATA-1 is associated with impaired erythropoiesis.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[22,23,25]

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. TAM is a disorder of fetalhematopoiesis[26,27,28].

The age at presentation is 2 days which is in concordance to what has been described in the literature. Liver, heart, bone marrow, pancreas and skin are the target organs damaged by the myeloblastinfiltration[29,30].The hematological findings commonly include presence of peripheral blasts, moderate leukocytosis and mild thrombocytopenia[30]

A bone marrow aspirate is not necessary as findings in marrow are less pronounced than those in the blood and add little towards diagnosis[31,32]. Morphology and immunophenotype of TAM blasts are similar to those of blasts in cases of AMKL. The blasts are large with basophilic cytoplasm with coarse granules and cytoplasmic blebs. Erythroid and megakaryocytic dysplasia is often present in bone marrow. The characteristics immunophenotype of TAM blast include positivity for CD34, CD117, CD13, CD33, CD41, CD42, CD36, CD61,CD7, CD4 dim, and negative for MPO, CD15, CD14 and glycophorin A.[33,34]

As GATA 1 mutations are the hallmark of the disease, peripheral blood cell should be analyzed for the mutations. Those harboring the mutations should be followed up every 3 months for the development of AMKL.

IV. Conclusion

TAM is a rare entity. In our case series, TAM presented within 3 days of birth. CD34, CD13, CD33, CD117, CD 7 and HLA-DR ???CD41,CD61 are useful markers for characterization of the TAM blasts.

TREATMENT

The treatment of TAM cases is usually supportive. However in infants with significant organ impairment therapeutic approaches to reduce the burden of blasts are used which include exchange transfusion, leukapheresis and chemotherapy[35] TAM cases with high blasts counts or liver dysfunction are given low-dose cytarabine [35,36,37].TMD blasts are highly sensitive to cytarabine, there is generally a rapid response with disappearance of blasts from peripheral blood in 36 days (median) [35]and normalization of blood counts in 84 days (median days)[36]

However, in TAM with severe liver disease associated with fibrosis the response to chemotherapy is poor and often is fatal. The factors associated with early death include hyperleukocytosis, hepatomegaly, deranged liver function tests, prematurity, ascites, coagulopathy and failure to normalize blood counts[35,36,37].

CONCLUSION

TAM is included in a differential diagnosis in a condition of presenting signs and symptoms of acute leukemia in neonates.It is a rare finding in congenital leukemia but awareness of TAM allows for early diagnosis and management to prevent progression to multiorgan failure. Lastly blasts should be tested for GATA1 to establish a definitive diagnosis.This allows for a family screening and good outcome of patient's health.

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