

Transient Abnormal Myelopoiesis in a Neonate without Down Syndrome

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Abstract

Transient abnormal myelopoiesis (TAM) also known as transient myeloproliferative disorder (TMD), a unique transient neonatal preleukaemic disorder characterized by clonal proliferation of megakaryoblasts, has been usually described to be associated with Down syndrome neonates. However, there are case reports of it occurring in neonates without Down phenotype, who are either mosaic for trisomy 21 or have trisomy 21 restricted to leukemic clone. This case report presents a case of TAM in a phenotypically normal neonate who presented in respiratory distress with features of tumour lysis syndrome (TLS) immediately after birth who was treated symptomatically and had spontaneous remission within three months.

Key words: Immunophenotype, morphology, transient abnormal myelopoiesis, trisomy 21, GATA1 gene, tumour lysis syndrome

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Introduction

Transient abnormal myelopoiesis (TAM) is a unique transient neonatal pre-leukaemic disorder characterized by clonal proliferation of megakaryoblasts that has mutation in GATA1 gene^{1,2}. TAM has wide clinical presentation ranging from incidental finding on blood film of healthy infant to critically ill neonate with multi organ failure^{3,4,5,6}.

The morphology and immune-phenotype of TAM blasts is highly variable¹. Spontaneous regression of blasts confirms the diagnosis of TAM⁷. Due to high chance of self-resolution, treatment is reserved for sick patients with life threatening features⁸. Patients who survive TAM should be regularly screened for development of leukaemia until age of 4-5 years⁸.

The Case

A term female infant, product of non-consanguineous marriage, weighing 2900 grams was born to 26 years old primi mother by caesarean section for leaking per vaginal. All antenatal visits were uneventful. There was no maternal history of radiation exposure, teratogens, and alcohol intake.

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Infant developed difficulty breathing immediately after birth. On examination, the infant had respiratory rate of 84/min with moderate subcostal retraction. She was afebrile without cardiovascular compromise. Oxygen saturation was maintained above 95% with oxygen. The abdomen was mildly distended, with hepatosplenomegaly. Neither dysmorphic features nor skin rashes were seen.

Initial laboratory reports revealed Haemoglobin: 15.2 gm/dl; Total Leukocyte Count: 1,36,000/cumm; Platelet count: 1,31,000/cumm; Peripheral smear: Atypical cells (16%), Myelocytes (12%), Metamyelocytes (10%), Neutrophil (40%), Lymphocytes (22%); CRP: 6mg/L; Blood group (mother and infant): "O" positive; Uric acid: 8.7mg/dL; Potassium: 6.1mEq/L; Sodium: 132 mEq/L; Calcium: 6.7mg/dL; LDH: 4626U/L; Total Bilirubin: 7.5mg/dL; Conjugated Bilirubin: 1.2mg/dL; SGOT: 120U/L; SGPT: 297U/L; ALP: 165U/L; Total protein: 4.51gm/dL; Albumin: 2.96gm/dL). Chest X-ray showed bilateral clear lung fields with normal cardiac shadow. Echocardiography revealed minimal pericardial effusion.

Laboratory parameters were consistent with hyper-leukocytosis with features of TLS. The infant was given supportive treatment with oxygen, intra-venous fluids, antibiotics, rasburicase, alkaline diuresis, oral aluminium hydroxide supplementation and Vitamin K by

injection. The infant showed gradual improvement and was transferred to mother's side on the fifth day.

IgM levels for congenital TORCH infection were negative. Bone marrow aspiration done on the third day of life revealed 36% blasts, 44% myeloid series cells, and 6% mature lymphocytes. Immuno-phenotyping of the blasts showed positivity for CD45, CD7, CD33, CD34, CD56 and CD117 and negative for CD1a, CD4, CD8, CD41, CD61, and cytoplasmic MPO. Karyotyping revealed 47 XX+21. GATA1 mutation analysis couldn't be performed.

Repeat blood investigations showed serial decline in blood counts and blasts % in peripheral smear with normalization by four weeks except for abnormal liver function test (LFT). The infant was discharged home on oral multivitamin supplements and ursodeoxycholic acid.

Bone marrow biopsy done at three months was normocellular for age with all normal haemopoietic elements. However, there was non-resolution of hepatosplenomegaly with persistent abnormal LFT. Doppler ultrasound of upper abdomen was within normal limits. Repeat karyotyping at three months showed absence of trisomy 21 and mutation in exon 2 of GATA1 gene was also not detected. Conservative management for cholestasis was continued. The infant was in morphological remission till six months

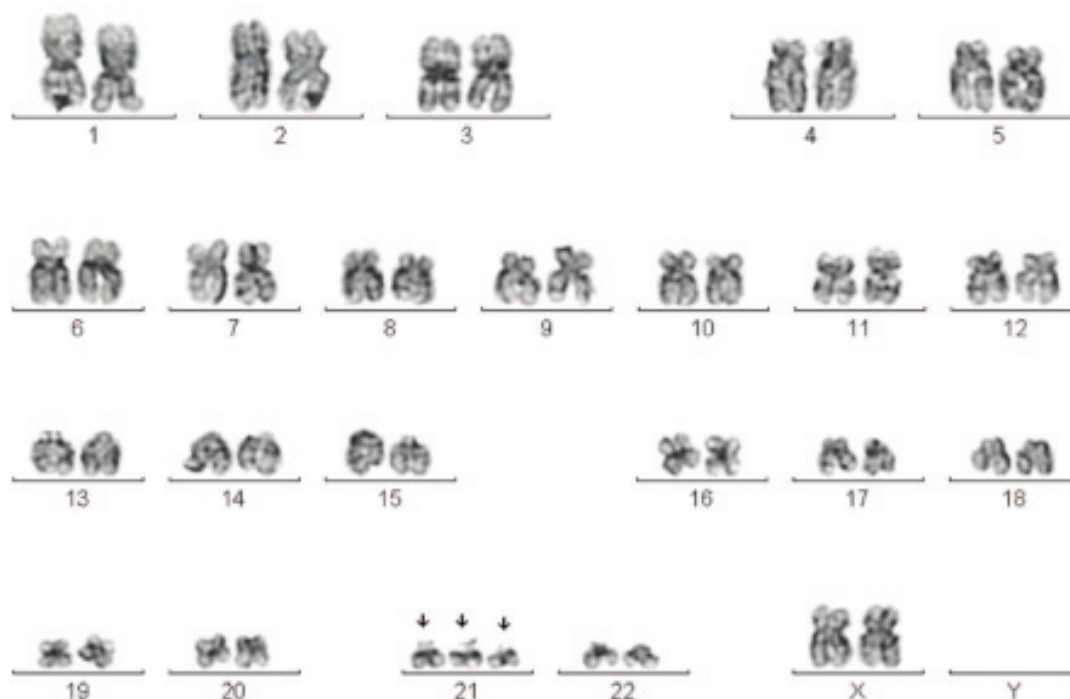


Fig 1: Chromosome analysis of patient showing female karyotype with trisomy 21.

Discussion

TAM, disorder of foetal haemopoiesis, is a rare clonal myeloproliferation with mutation occurring in either immature myeloblasts or megakaryoblasts lineages corresponding to FAB M0 or FAB M7 respectively^{3,8,9,10}. Two distinct genetic events implicated in the pathogenesis of TAM are: trisomy 21 and somatic mutation of X-linked GATA1 gene, negative regulator of megakaryocytic proliferation¹⁰. Presence of GATA1 mutation is considered as hallmark of the disease, which disappears during remission^{1,2,10}.

TAM blasts are typically described as megakaryoblastic with cytoplasmic blebbing, and agranular basophilic cytoplasm^{1,10}. The immune-phenotyping of TAM blasts include positivity for CD34, CD117 (stem cell markers); CD13, CD33 (myeloid markers); CD41, CD42, CD36, CD61 (megakaryoblastic markers); CD4, CD7, CD56 (no lineage markers)^{2,8,10,11}. However, the morphology and the immune-phenotype of TAM blast cells is highly variable¹. The morphology and immune-phenotyping of blasts in presented case had resemblance to minimally differentiated Acute Myeloid Leukaemia (FAB M0) in contrast to typically described Acute Megakaryocytic Leukaemia (FAB M7).

TAM is reported to occur in up to 10% of neonates with Down syndrome^{2,9,10,12}. While its true incidence being undetermined, it can also occur in phenotypically normal neonates who are either mosaic for trisomy 21 or have acquired trisomy restricted to the leukemic clone^{11,13}. Although, the clinical presentation of the TAM can be highly variable, most of infants have mild clinical course^{1,10,11}. The median age of disease presentation is 3-7 days with almost all cases occurring by two months^{2,8}. The most common antenatal finding noted is severe hepatomegaly⁸. Clinical features include hepatomegaly (being second most common after peripheral blasts), splenomegaly, cholestasis, jaundice, pericardial/pleural effusion, ascites, respiratory distress, and bleeding diathesis^{2,10,11}. Very few cases of TAM with TLS are reported, the presented case being one of them¹⁴.

The laboratory findings commonly include leucocytosis, increased peripheral blasts with mild thrombocytopenia^{1,2,10}. Hyperleukocytosis with peripheral blasts and mild thrombocytopenia was present in this case. Risk factors for early mortality include: WBC counts >100,000/uL, preterm delivery, effusions (pleural, pericardial, ascites, or hydrops), coagulopathy, bleeding diathesis, platelet count <100,000/uL, low birth weight and failure to clear peripheral blasts and normalize blood counts^{2,10}.

TAM should be differentiated from leukemoid reaction, erythroblastosis foetalis, congenital infections, and congenital leukemia¹⁵. When TAM is suspected, cytogenetic karyotyping analysis and GATA1 mutation analysis are recommended^{2,11}. Karyotyping performed initially in presented case showed 47, XX+21 which later revealed 46, XX when the infant went in morphological remission suggesting that trisomy 21 was restricted to blasts/leukemic clone. Though GATA1 mutation analysis couldn't be performed initially, was negative when performed later during morphological remission.

Confirmation of diagnosis of TAM occurs at time of spontaneous regression, which can take place weeks or months after presentation⁷. Complete remission is often characterized first by normalization of blood counts and disappearance of peripheral blasts followed by resolution of clinical symptoms such as hepatomegaly¹⁶. Most neonates with TAM ($\geq 80\%$) undergoes spontaneous remission within 3-6 months of age^{2,8,11} whereas 10-30% patients develop acute megakaryocytic leukaemia (AMKL) within first five years of life^{1,2,3,9,13}. Patient who survive should be followed up regularly with complete blood count and differential counts approximately every 3-6 months until age of 4-5 years^{8,11}.

Treatment of TAM is usually supportive. Cholestatic liver disease is managed with adequate nutrition, fat-soluble vitamin supplement and ursodeoxycholic acid^{10,11}. In infants with one or more life threatening features, treatment is advised^{3,11}. Therapeutic options include exchange transfusion, leukapheresis, and chemotherapy¹⁰. As this patient showed gradual improvement with symptomatic treatment, no other therapy was given. TAM blast cells are highly sensitive to cytarabine, which is given at dose of 0.5-1.5mg/kg for 3-12 days^{1,4}. The presence of hepatic dysfunction significantly decreases the success rate of chemotherapy^{8,16}.

The overall mortality is reported to be ~20% but only ~10% deaths are TMD related^{1,3,10}. Death due to TAM is usually due to hepatic failure secondary to fibrosis and blasts cell infiltration¹.

Conclusion

Even in a phenotypically normal neonate with leucocytosis, TAM is one of the important differential diagnoses to consider apart from sepsis. Karyotyping and GATA1 mutation testing help to reach the diagnosis. Regular follow up of the patient till 5 years is advisable for detection of acute leukaemia.

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