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CASE REPORT

Transient Myeloproliferative Disorder and Down Syndrome

Is there a link?

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اضطراب التَكاثري النِقْيِيّ المؤقت ومتلازمة داون

هل ثمة رابط؟

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الملخص: عُرِضَ علينا وليد ذكر خديج للغاية مصاب باضطراب غير عادي في أجهزة الجسم المتعددة خلال اليومين الأوليين من حياته. وقد بيّنت الأحداث السريرية والفحوصات اضطراب التكاثري النقي المؤقت. وقد كان ذلك الاضطراب السبب الرئيسي للتنميط النووي لهذا الرضيع الخديج بدون وجود وصمات مميّزة لمتلازمة داون. معرفة وجود اضطراب التكاثري النقيي المؤقت لدى وليد تستوجب التنميط النووي بحثا عن التثلث الصبغي 21، والترصّد الدقيق للحالة وذلك لإمكانية تطوره إلى ابيضاض الدم.

مفتاح الكلمات: اضطراب التكاثري النقيّ المؤقت، متلازمة داون الفسيفسائية، ابيضاض الدم النقوي الحاد، تقرير حالة، عُمان.

ABSTRACT: An extremely premature male neonate presented with an unusual multisystem dysfunction within the first 24 to 48 hours of life. The unfolding of clinical events and investigations revealed a transient myeloproliferative disorder (TMD). TMD was the main indication for karyotyping of this premature infant without clinical symptoms of Down syndrome. The awareness of TMD in a newborn warrants karyotype analysis to look for trisomy 21 and a close surveillance because of its potential progression to true leukaemia.

Keywords: Extreme premature; Transient myeloproliferative disorder; Down syndrome; GATA1; Acute myelogenous leukemia (AML); Case report; Oman.

The classic features of Down syndrome (DS) may not initially be apparent in extremely premature newborns. Rarely, DS will present in association with a haematologic entity referred to as transient myeloproliferative disorder (TMD), also known as transient leukaemia (TL). TMD can be self-limiting with an estimated incidence of 10% in patients with DS. However, in 20–30% of cases it may transform to true leukaemia.[1,2] We report an extremely premature neonate with mosaic Down syndrome (MDS) who appeared phenotypically normal and presented with multisystem dysfunction, TMD, and subsequently developed acute myeloid leukaemia (AML).

Case Report

A male neonate was born at 26 weeks of postmenstrual age to non-consanguineous parents. The mother was a 31-year-old known asthmatic G7P6A1. Her intrapartum course was complicated by *placenta abruptio*; hence, the baby was born by an emergency Caesarean section and the mother lost a litre of blood during delivery. In view of the neonate's poor general condition and marked pallor at birth, immediate resuscitation and ventilatory support were rendered. The right hand was noticeably blanched and had turned cyanotic. The radial and ulnar pulses were not palpable. There were no apparent dysmorphic features. The growth parameters were adequate for gestational age; the baby's birth weight was 1,020 gr, body length was 34 cm, and head circumference 24 cm. In the first 24 to 48 hours of life, the baby had

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Table 1: Serial complete blood count (CBC)/peripheral smear (PS)

	Day 0	Day 1	Day 5	Day 10	Day 14	Day 20
RBC 10^{12}/L	1.72	2.32	4.38	4.29	5.35	4.05
Haemoglobin gm/dL	6	9.3	13.7	11.6	12.8	10.2
Haematocrit L/L	0.17	0.27	0.39	0.34	0.40	0.31
MCV fL	101	116	88	80.3	74.9	75.7
MCH pg	35.1	40.5	31.3	27.0	23.9	25.1
MCHC g/L	34.9	34.8	35.5	33.7	31.9	33.2
RDW %	27.3	20.2	20.7	24.2	22.5	21.9
NRBC 10^9/L	0.9	4.6	0	0.4	0.4	0
Platelet count 10^9/L	21	328	309	119	301	67
WBC 10^9/L	8.6	44.9	56.7	59.6	36.9	11.4
Neutrophils 10^9/L	2.3	5.2	22.8	43.9	27.1	5.2
Lymphocytes 10^9/L	5.4	21.2	21.7	12	8.1	5.2
Monocytes 10^9/L	0.9	17.2	11.9	3.6	1.5	0.9
Eosinophils 10^9/L	0.1	1.2	0.2	0.2	0.1	0
Basophils 10^9/L	0	0.1	0.1	1.1	0	0
Retics %	4.2	5.8	2.3	0.8	1.1	0.8
Retics absolute	71.6	145	102	46.7	60.7	31.7
Peripheral smear: presence of blasts cells (<15%)	+	+	+	+	+	+

RBC = red blood cells; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; RDW = red blood cell distribution width; NRBC = nucleated red blood cells; WBC = white blood cells.

severe respiratory distress syndrome (RDS) that was treated with a surfactant. The major concern then was the apparent vascular compromise of the right hand, but there was no identifiable reason for the condition. Heparin was administered for a few hours and discontinued when the neonate's activated partial thromboplastin time (APPT) rose to 180 seconds. The right hand became pink on the 4th day and his pulses returned to normal by the 12th day. The possibility of feto-maternal haemorrhage as the cause of the neonate's marked anaemia (haemoglobin 9.3 gr/dl) was unproven.

The skin was thick and marked by scattered vesiculopustular lesions in the perianal area. Evaluation of and treatment for infection was indicated by the probability of a staphylococcal sepsis. Weekly blood cultures in the first 6 weeks of life and a culture of the skin lesions for bacterial and viral infections such as cytomegalovirus (CMV), herpes, parvovirus, mumps, and enteroviruses were negative. The skin appeared normal after 2 to 3 weeks.

The initial complete blood count (CBC) from the cord sample showed pancytopenia. The trend of the serial CBC during the first two weeks of life showed leukocytosis of 30–59 x 10^9/L and an absolute neutrophil count (ANC) of 10–37 x 10^9/L. His platelet count decreased from day 20. Blast cells were seen on the peripheral smear on the first day of life [Table 1]. The leukaemia immunophenotyping done on the third day of life revealed that the blasts were CD 13, 33, 34, 117 and HLA-DR positive, consistent with acute myeloid leukaemia (AML), and were negative for lymphoid markers [Figure 1]. These immature blast cells were considered unique to prematurity or possibly secondary to trisomy 21. The diagnosis of TMD was based on the persistence of blast cells on serial peripheral smears beyond one week of life [Figure 1]. Earlier physical examinations had shown no clinical features consistent with DS. However at about 33 weeks of gestation, a few features, such as epicanthal folds and the low nasal bridge of DS, were noticeable. The cytogenetic analysis revealed MDS 47,XY,+21/46, XY.

On the second day of life, the baby developed intractable segmental myoclonus characterised as spontaneous and stimulus-sensitive, and involving the palate, and upper and lower limbs. The seizures were controlled completely on the third week with triple anticonvulsants, namely phenobarbital, phenytoin, and levetiracetam. The electroencephalogram (EEG) showed a burst-suppression-like pattern with spike-and-wave discharges. There were no structural abnormalities or thrombosis identified on a magnetic resonance imaging (MRI) scan of the brain.

The comorbidities that arose during the baby's adverse clinical course were the following: bronchopulmonary dysplasia (BPD); Stage 2 Zone II retinopathy of prematurity (ROP) that required laser therapy; cholestasis, and osteopenia of prematurity (OOP).

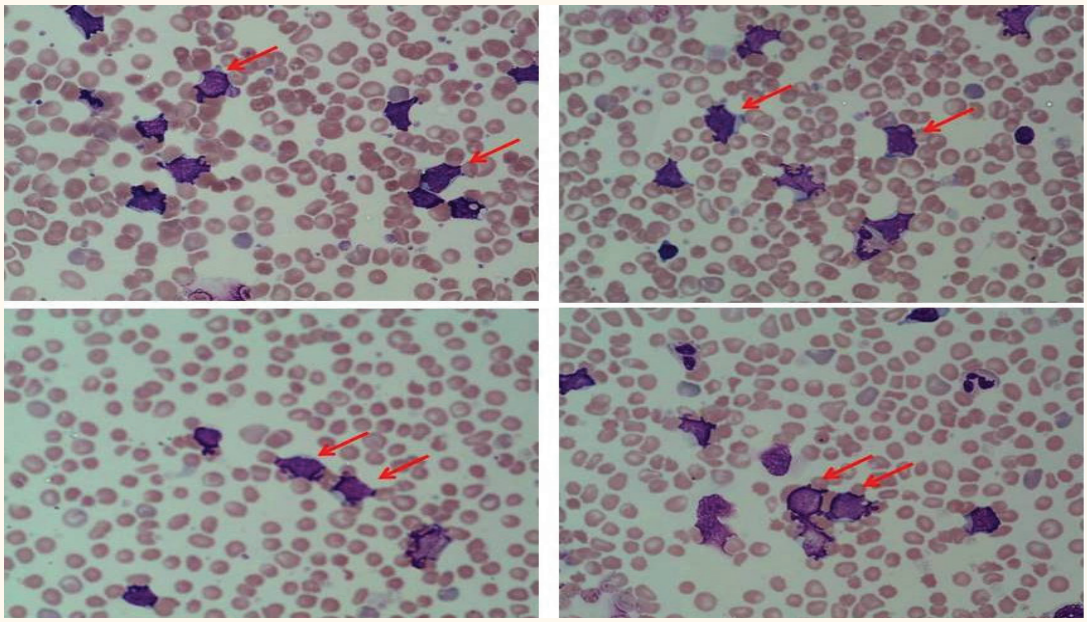

Figure 1: Peripheral smears in the first 2 weeks of life, with blasts cells indicated by red arrows.

He was discharged at 85 days of life with growth parameters below the 3rd centile; he weighed 2,160 gr, and was 42 cm in length, with an HC of 29 cm. The baby's subsequent follow-up would prove to be critically important given his history of TMD. The monitoring protocol used was a CBC every 3 months. The haematological problem resolved at 6 months of age. There were difficulties encountered in obtaining an adequate specimen from serial bone marrow aspirates (BMA) at 6 months and 16 months. The findings each time showed no leukaemic markers. However, in the presence of progressive hepatosplenomegaly (HSM) from 16 months of age, a repeat BMA at 17 months of age confirmed the finding of AML [Figure 2]. His immunophenotype by flowcytometry showed a biphenotypic leukaemia with positive lymphoid and myeloid markers, with a predominance of the latter. He was treated using the 2007 treatment protocol for AML-DS, which consisted of a total of four courses of chemotherapy, with two induction courses followed by two consolidations. The chemotherapy in the induction course included cytarabine, idarubicin, etoposide, and intrathecal cytarabine. In the consolidation phase, the chemotherapy included high dose cytarabine and mitoxanthrone. Presently, the baby is 3 years old and has been in remission since 2 years of age.

Discussion

DS is the most common recognised chromosomal abnormality, occurring in 1: 1000 live births. Full trisomy 21 presents in 94% of patients, MDS in 2.4%, and translocations in 3.3%.3 In MDS, there are two populations of cell lines—a normal cell line with 46 chromosomes and a second line with trisomy 21. In patients with MDS, clinical features vary from normal to subtle to full expression of DS depending on the level and distribution of the trisomic cells within the tissues.4 Our patient was a confirmed case of MDS who initially presented without clinical features of DS.

All cytogenetic types of DS are predisposed to develop leukaemia. Approximately 10% of people with DS present with TMD and, after initial resolution, a significant proportion (20–30%) may subsequently develop any of the following: acute myelogenous leukaemia (AML), acute lymphoblastic leukaemia (ALL), or acute megakaryocytic leukaemia (AMKL). More recent studies have implicated the mutagenesis of haematopoietic transcription of factor gene GATA 1 as an initiating agent in DS leukaemogenesis.[5] The GATA 1 gene, located on the X chromosome, encodes a zinc-finger transcription factor that is essential for normal erythroid and megakaryocytes differentiation. Somatic mutations in exon 2 of GATA1 have been detected exclusively in trisomy

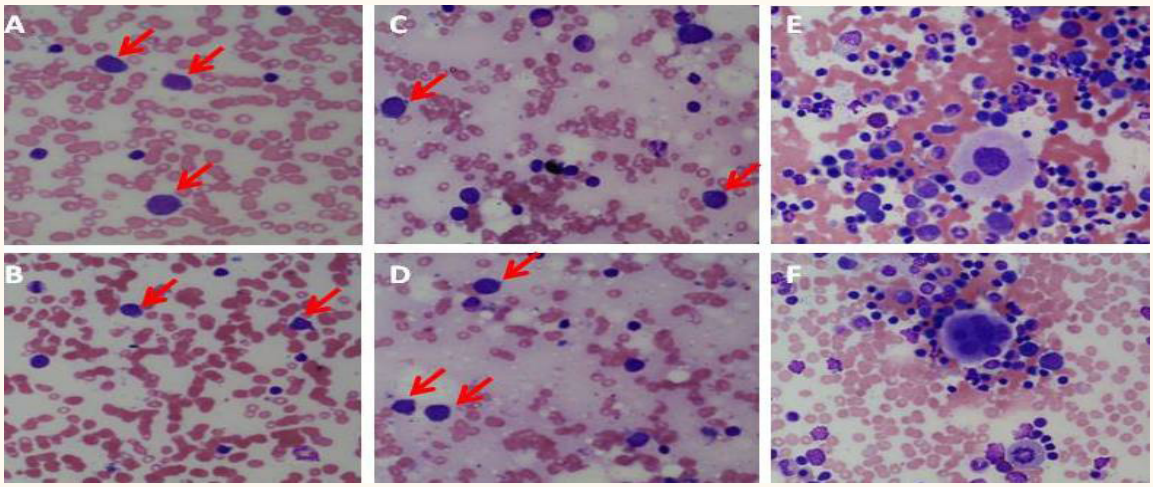

Figure 2: Serial bone marrow aspirates (BMA) images with blasts cells at 17 (**A**), 18 (**B**), 19 (**C**), and 22 (**D**) months of age. Please note the absence of blast cells at 22 months when the patient was in remission **(E & F)**.

21-associated TL as well as non-DS related AMKL.

There are three cooperating events in pathogenetic steps in AML-DS: trisomy 21, the GATA1 mutation (GATA1s), and an undefined genetic alteration. However, it remains unclear which factors in the chromosome 21 cooperate with the oncogenic GATA1s and which factors drive this transition from preleukaemia to AML-DS. The blast cell sensitivity to chemotherapy in AML-DS has been linked to the gene-dosage effect of chromosome 21 localised genes that leads to an increased level in the expression of cystathionine beta-synthase, contributing to cytarabine sensitivity. The generation of GATA1s results in interactions and modulation of the expression of different genes, such as the cytidine deaminase gene (CDA) localised to chromosome 1. CDA is involved in the irreversible hydrolytic deamination of ara-C (cytarabine) to the inactive ara-U (uracil). The expression of anti-apoptotic proteins such as BCL2 (whose gene, BCL2, is localised to chromosome 18), and HSP70 (whose gene, HSP70, is localised to chromosome 5) is lower in DS AML blasts, suggesting that DS megakaryoblasts are more susceptible to chemotherapy-induced apoptosis. Overexpression of CBS has been correlated with *in vitro* generation of ara-CTP, the active intracellular ara-C metabolite, and subsequent increased ara-C sensitivity in DS AML blast cells.[6]

Our patient was diagnosed with TMD on the basis of the 6-month persistence of blast cells, and its resolution was based on serial BMA findings negating the presence of leukaemia. However, the presence of hepatosplenomegaly at 16 months indicated that the TMD was not transient and had progressed to AML. The difficult in aspirating specimens in the earlier BMAs may have been due to hypercellularity and myelofibrosis, an antecedent myelodysplastic phase. Extreme prematurity, significant early leukocytosis, and the reappearance of blast cells after an apparent resolution were considered risk factors for the progression to true leukaemia.

The appearance of the neonate's right hand at birth gave rise to major concerns about an acute vascular compromise or a thromboembolic episode. Neonates are particularly susceptible to thromboembolic diseases because of the relative immaturity of the homeostatic system and the potential presence of serious underlying disease.[7] Investigations to identify its cause ruled out congenital and acquired thrombophilia, and cyanotic heart disease. The right hand may have been entrapped during delivery, leading to an acute arterial vasospasm. The surveillance for the long term effects of this event showed no disparity in growth of the upper limbs.

There are many possible causes of vesiculopustular eruptions in babies, but the commonest is infection. Its appearance in our patient coincided with leukocytosis, and persistence of blast cells. Whether these lesions represented the leukaemic cutis associated with TMD was

something that was not investigated.[7] There are reports in the literature of neonates presenting with TMD and cutaneous lesions without morphologic features of DS that were proven to have MDS.[8–10] In hindsight, both the unusual slow-healing skin lesions and TMD should have served as clues to the identification of DS in the baby. The early development of intractable seizures was considered hypoxia-induced due to the neonate's severe anaemia at birth.

Conclusion

Neonates, especially extremely premature babies, with an easily recognised syndrome like DS may not present initially with significant physical features; however, DS may present as its rarest associated clinical problem, TMD.

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