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Case Report OMICS International

Transient Myeloproliferative Disorder in Neonate with Suspected Down Syndrome

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Patient Presentation

A female with suspected Down syndrome was born by vaginal delivery at 37 weeks 2 days' gestation to a mother with a history of Type A2 gestational diabetes mellitus. Routine prenatal testing consisted of a non-invasive screening test for aneuploidy. Results, presented in Table 1, indicated an aneuploidy for trisomy of chromosome 21, indicating an increased risk for Down syndrome. Prenatal confirmatory testing was declined. An ultrasound performed at 20 weeks, 2 days showed an absent nasal bone, unilateral choroid plexus cyst, borderline thickening of nuchal fold, and bilateral pyelectasis. These ultrasound findings are markers for aneuploidy, and increase the risk for fetal genetic syndrome [1]. A fetal echocardiogram was performed at 36 weeks and indicated that there was a possible coarctation of the aorta. Based on the positive aneuploidy screening and ultrasound results, Down syndrome with potential congenital heart defects was suspected.

Condition	Results	PPV or Residual Risk
Trisomy 21 (Down Syndrome)	Positive: Aneuploidy Detected Results consistent with trisomy for chromosome 21	35.76% (35.76 in 100) PPV
Trisomy 13 (Patau Syndrome)	Negative Results consistent with two copies of chromosome 13	<0.01% (1 in 10,000) Residual Risk
Trisomy 18 (Edwards Syndrome)	Negative Results consistent with two copies of chromosome 18	<0.01% (1 in 10,000) Residual Risk

Table 1: Patient's prenatal Aneuploidy screen.

Post-delivery, an Apgar test was performed. Apgar scoring is a rapid method of evaluating the overall health status of infants directly after delivery and assesses the need for resuscitation. A score of 0-10 is given after evaluating color, heart rate, muscle tone, reflexes, and respirations. The Apgar score at 1 minute was 8, and was 9 at 5 minutes, consistent with good physiologic condition post-delivery. The neonate was transferred to the NICU to monitor blood sugar and repeat the fetal echocardiogram. Bedside glucose levels were performed on the neonate on Day 1 due to the mother's gestational diabetes mellitus and are presented in Table 2. Gestational diabetes mellitus can cause hypoglycemia of the neonate as the neonate increases insulin production due to consistently high glucose levels delivered from the maternal blood supply. The neonate's blood glucose level was within normal range, indicating appropriate insulin production. The echocardiogram on Day 1 revealed a large patent ductus arteriosus, along with evidence of either a stretched patent foramen ovale or small atrial septal defect. There was no evidence of coarctation of the aorta. Patent ductus arteriosus, patient foramen ovale, and small atrial septal defects are known to close on their own and did not require immediate intervention. Follow up with cardiology as outpatient was recommended.

Test	Day 1 0036	Day 1 0442	Day 1 1020	Day 3	Reference Range	Units
POC Glucose	58	48	56	-	30-60	mg/dL
Total Bilirubin	-	-	-	11.1	6.0-7.0	mg/dL

Table 2: Patient's chemistry test results.

Upon physical examination on Day 3, the patient appeared to be active, alert, and in no acute distress. The patient had a temperature of 99.2°F, pulse was 104, with a respiratory rate of 39 breaths per minute. The patient latched, fed, voided, and stooled well. The head was atraumatic and normocephalic. Examination of the neck showed increased skin in the neck fold. Examination of the eyes showed an upward slanting eye with a prominent inner canthus. Ears and nose were patent. Cardiovascular exam revealed a regular rate and rhythm and no murmur. Musculoskeletal exam revealed a spinal dimple, but was otherwise unremarkable. Respiratory, abdominal, genital exams were unremarkable. Dermatological exam was normal for the patient's ethnicity and no jaundice was noted.

Total bilirubin levels were ordered on Day 3 and results are presented in Table 3. Total bilirubin levels were ordered to assess hyperbilirubinemia and the risk of kernicterus and results are presented in Table 3. Kernicterus is a condition caused by hyperbilirubinemia that overcomes the threshold of the blood brain barrier, crosses and causes neurological damage. Hyperbilirubinemia can also be a finding in Down syndrome patients with transient myeloproliferative disorder (TMD) [2]. The patient was found to have an elevated total bilirubin at a level associated low intermediate risk of kernicterus.

Test	Result	Reference Range	Units
White Blood Count	21.1	9.0-30.0	K/uL
Red Blood Count	6.17	4.70-6.10	M/uL
Hemoglobin	20.7	13.5-19.5	g/dL
Hematocrit	58.6	40.0-65.0	%
Mean Corpuscular Volume	95.0	98.0-118.0	fL
Mean Corpuscular Hemoglobin	33.5	28.0-36.0	pg
Mean Corpuscular Hemoglobin Concentration	35.3	30.0-36.0	g/dL
Red Cell Distribution Width	22.2	11.5-14.5	%
Platelet Count	85	140-500	K/uL
Immature Granulocyte % (Auto)	6.3	-	%
Neutrophils % (Auto)	44.4	-	%
Lymphocytes % (Auto)	17.1	-	%
Monocytes % (Auto)	30.3	-	%
Eosinophils % (Auto)	0.9	-	%
Basophils % (Auto)	1.0	-	%
Nucleated RBC Relative Count (Auto)	2/100	-	-
Immature Granulocyte # (Auto)	1.32	-	K/uL
Lymphocytes # (Auto)	3.61	2.00-11.00	K/uL
Monocytes # (Auto)	6.38	0.00-3.50	K/uL
Eosinophils # (Auto)	0.18	0.00-0.45	K/uL
Basophils # (Auto)	0.22	0.00-020	K/uL
Segmented Neutrophils % (Manual)	50	-	%
Band Neutrophils % (Manual)	3	-	%
Lymphocytes % (Manual)	18	-	%
Monocytes % (Manual)	6	-	%
Eosinophils % (Manual)	0	-	%
Metamyelocytes % (Manual)	3	-	%
Myelocytes % (Manual)	1	-	%

Blast Cells % (Manual)	19	-	%
Immature Granulocytes	Present	-	
Absolute Neutrophil	12.03	6.00-26.00	K/uL
Nucleated RBC/100 WBC	3/100	-	-
Platelet Estimate (Manual)	Adequate	-	-
Polychromasia	1+	-	-
Anisocytosis	Present	-	-

Table 3: Results of patient's hematology testing.

Laboratory testing also included a complete blood count (CBC) on Day 3 presented in Table 3. A CBC was ordered to assess the state of the peripheral blood as there are many hematological manifestations associated with Down syndrome. The CBC results showed polycythemia and thrombocytopenia, both hematological findings in Down syndrome neonates. Blasts observed in the peripheral smear were confirmed by hematopathology, and a diagnosis of transient myeloproliferative disorder associated with Down syndrome was made based on the presence of circulating blasts only.

The patient was discharged on Day 3 in the care of her mother with diagnoses of suspected Down syndrome with associated patent ductus arteriosus, stretched patent foramen ovale or small atrial septal defect, TMD, polycythemia, and thrombocytopenia. A cord blood sample was sent to a reference laboratory for chromosomal analysis to confirm trisomy 21, but testing was unable to be completed due to an insufficient number of suitable metaphases. The prenatal testing, physical exam findings, and echocardiogram findings support a diagnosis of Down syndrome, but a definitive diagnosis is contingent upon chromosomal analysis. The clinical plan included follow-up with cardiology as an outpatient to monitor the congenital heart defects. The thrombocytopenia and polycythemia were to be followed up by CBC at 3-month check-up, or sooner if symptoms develop. Instructions were to recheck the CBC at 3-month intervals to age 3 and every 6 months until age 6 to monitor the transient myeloproliferative disorder, per American Academy of Pediatrics guidelines. It was also advised that the patient receive a hematology/oncology consult after the cardiology and other consults have been resolved.

Upon cardiology follow up on Day 12, the patient was showing no cardiovascular signs or symptoms. The cardiovascular exam showed a regular rate and rhythm with a soft grade systolic murmur noted along the left lower sternal border. Exam of the extremities revealed strong peripheral pulses; the extremities were warm to the touch and appeared well perfused. No clubbing, cyanosis, or edema was evident. Echocardiogram results revealed a patent ductus arteriosus and a patent foramen ovale. As patent ductus, arteriosus and patent foramen ovale have a high likelihood of closing on their own, immediate treatment was not warranted. Follow up with a repeat echocardiogram in 3 months was recommended.

Discussion

Down syndrome is a chromosomal disorder, affecting chromosome 21. Ninety-five percent of Down syndrome patients have non-familial trisomy 21, a condition where there are 47 total chromosomes and one extra copy of chromosome 21. Infrequent causes of Down syndrome include translocation of chromosome 21 and mosaic Down syndrome [3]. The excess genetic material carried by the additional chromosome causes developmental changes in utero causing intellectual delays. Multiple organ systems are affected including cardiac, respiratory, musculoskeletal, hematologic, gastrointestinal, and the endocrine. Congenital heart defects are the most common defect among patients with Down syndrome, with approximately 50% of patients affected [3]. Of those affected, atrial septal defects were found to be the most common, while patent ductus arteriosus comprised of approximately 6% of congenital heart defects [4].

In addition to the congenital heart defects, hematological manifestations are also a common finding, with polycythemia affecting 18% to 64% of Down syndrome patients [3]. TMD, also known as transient abnormal myelopoiesis, is found in approximately 4% to 10% of neonates with Down syndrome. TMD is virtually exclusive to the Down syndrome population. Characteristic findings include circulating blasts in peripheral blood with possible thrombocytopenia (40%) and/or leukocytosis (20% to 30%) [5].

The pathophysiology of TMD involves a number of hematopoietic gene mutations that ultimately result in the characteristic hematological findings in TMD. While many genes are affected, the most notable is the *GATA1* gene, which is a hematopoietic transcription factor. *GATA1* is found on the X chromosome and is necessary for normal erythropoiesis and differentiation of the megakaryocytic lineage. Under normal physiological conditions, megakaryoblasts are confined to the bone marrow and undergo differentiation to megakaryocytes. Megakaryocytes produce thrombocytes, which are released into the peripheral blood. In TMD, a somatic mutation at exon 2 leads to a truncated version of the *GATA1* gene, GATA1s [6]. The *GATA1*s gene mutation blocks differentiation of the megakaryocytic lineage past the megakaryoblast stage [7]. The lack of differentiation results in increased circulating blasts and thrombocytopenia. Neither *GATA1* mutations in patients without Down syndrome or Down syndrome with wild type *GATA1* have associated TMD [7,8]. One study showed a trisomy-21-associated upregulation of *GATA1*s expression leading to a proliferation of megakaryoblasts; demonstrating a definite link between Down syndrome and TMD and possibly synergistic interaction [8].

A defining feature of TMD is that is that the circulating blasts are transient, and most cases of TMD resolve spontaneously within 3-6 months without treatment. Signs that may warrant treatment are organomegaly, cardiac, hepatic or renal failure. Treatment is aimed at reducing the number of circulating blasts and usually involves low dose cytosine arabinoside, an antineoplastic drug effective against

megakaryoblasts. While treatment may decrease the circulating blast count in TMD, it does not decrease the risk of developing acute myeloid leukemia (AML) [9].

Even with patients with spontaneous resolution, TMD is associated with future risk of AML and increased mortality. Patients with Down syndrome have a 500-fold increased risk of developing acute megakaryocytic leukemia (AMKL) compared to the general population while Down syndrome patients with a history of TMD have a 20% to 30% rate of progression or future development of acute myeloid leukemia (AML), most often AMKL [7]. Gamis et al. found that time to resolution of TMD was the only statistically significant factor in the development of AML. The study showed that patients whose TMD resolved after the median time of resolution (47 days) had a greater risk of developing AML compared to patients whose TMD resolved before the median time of resolution [10]. There is an approximately 10% mortality rate from complications arising from TMD [5]. The patient's age at diagnosis and presence of renal dysfunction appear to play a role in risk of mortality, while congenital heart disease and leukocytosis were found to be more prevalent in patients who expired, they were not considered a statistically significant risk of mortality [9].

The patient's prognosis is dependent on many factors, including non-hematologic manifestations of Down syndrome and time to resolution of TMD. Most cases of TMD spontaneously resolve and do not develop into future AMKL.

Conclusion

The patient was suspected to have Down syndrome, which is a common genetic disorder worldwide. The patient presented with circulating blasts in the peripheral blood, and was diagnosed with TMD, as well as congenital heart defects associated with Down syndrome. Down syndrome can affect many organ systems and there is a variety in symptoms and severity. This patient has specific disorders that are less common in Downs syndrome patients including TMD and patent ductus arteriosus. TMD is a relatively uncommon disorder associated with Downs syndrome and affects approximately 10% of patients. Congenital heart defects are common in patients with Down syndrome, but this patient's patent ductus arteriosus is found in approximately 6% of patients and was compounded with a second congenital heart defect.

In conclusion, TMD is an uncommon hematologic disorder associated Down syndrome. Even though most cases spontaneously resolve, an increased risk of progression to AMKL compared to the normal population; along with mortality rate, which is compounded by other organ system involvement, makes TMD a condition that should not be overlooked in the Down syndrome patient.

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