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Transient Myeloproliferative Disorder in a Neonate without Down Syndrome—A Rare Case Report and Review of the Literature

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Abstract

Transient myeloproliferative disorder (TMD) is a self-limiting disorder characteristically seen in neonates with Down syndrome with or without somatic mosaicism. Trisomy-21 limited to the hematopoietic lineage alone has been described; awareness of which is very important for appropriate evaluation and counseling in phenotypically normal children.

We report a newborn with TMD who presented at birth with intracranial bleed secondary to thrombocytopenia. Peripheral smear showed 10% blasts and flow cytometry further revealed myeloid blasts of megakaryocytic lineage. The child had no phenotypic features of Down syndrome.

Cytogenetic analysis (fluorescence in situ hybridization) and the conventional karyotyping from peripheral blood showed trisomy-21 in blast cells and the findings completely cleared with peripheral clearance of blasts. The possibility of Down syndrome with mosaicism was considered, however, repeat conventional karyotyping from peripheral blood at D36 and D60 of life was normal, suggesting the gain of chromosome 21 was restricted to the TMD clones.

The child was supported with irradiated platelet transfusions and adequate hydration. Spontaneous resolution with resolution of cytopenias and peripheral clearance of blasts were noted from D10 of life. The child is neurologically normal and growing well.

Very few reports of TMD in newborn babies without Down syndrome have been described in the literature. Awareness about the diagnostic entity of TMD even without Down syndrome would help in appropriate management and counseling.

Keywords

- congenital leukemia
- Down syndrome
- mosaicism
- transient abnormal myelopoiesis
- case report

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Introduction

Transient myeloproliferative disorder (TMD), a transient clonal proliferative disorder usually of megakaryocytic lineage, is often associated with Down syndrome (DS) babies.[1] The natural history of TMD and genetic landscape is well-described entity. Two-thirds of children with DS and TMD would resolve spontaneously; however, 30% of children carry a risk of developing acute myeloid leukemia (AML)-M7 within 5 years of life.[1] DS with somatic mosaicism has been brought to light with a diagnosis of TMD at birth.[2] TMD with the absence of features of DS and constitutional karyotypic abnormalities is meagerly reported in the literature.

Case Report

We report a term male neonate, born to 34-year primigravida with no significant antenatal concerns, who had hematoma in the occiput and irritability immediately after birth. The child was delivered by assisted vaginal delivery with forceps. The child also had focal seizures at birth and required intensive care monitoring and antiepileptics. The baby was lethargic, had ecchymotic patches in the trunk, and had hepatosplenomegaly. No dysmorphism or external anomalies were present. The baby had generalized hypotonia at birth with absent neonatal reflexes. Complete blood count showed hemoglobin level 15.2 g%, total white blood cell count (WBC) 35,930/mm^3 with differentials including 20% neutrophils, 67% lymphocytes, and blasts 10%; and platelet count was 35,000/microliter. Sepsis screen was negative. LDH level was 1,625 units/L and uric acid was 1.9 mg%.

Computed tomography brain showed hemorrhage in the right superior cerebellar, bilateral tentorial, and posterior inter-hemispheric regions, and a midline occipital bone fracture with a diffuse occipital and bilateral high parietal subglial hematoma. Flow cytometry from peripheral blood revealed 21.6% abnormal myeloid blasts (positive for CD117, CD33, CD36, CD34, CD41, CD71, HLA-DR, and CD42a). Fluorescence in situ hybridization showed Trisomy-21. Karyotyping revealed mosaicism with 50% cells showing trisomy-21 and 50% a normal karyotype. The working diagnosis was TMD; in view of no phenotypic features of DS as per Hall's criteria,[3] the possibility of DS with mosaicism confined to blast cells was considered. The baby was supported with irradiated blood products, antiepileptics, and supportive care. With supportive care the child's neurological parameters improved, gradually but spontaneously the hematological parameters also improved.

Hepatosplenomegaly regressed and peripheral blasts cleared by day 20 of life. WBC and platelet counts normalized completely by day 36 of life. Repeat karyotyping done twice on Day 35 and Day 60 of life revealed a normal chromosome complement. No other clinical features of DS were present and child is attaining milestones normally with normal neurological findings on follow-up for the past 8 months.

Discussion

TMD or transient abnormal myelopoiesis is a clonal disorder of megakaryocytic lineage in the neonates, characteristically differentiated from congenital leukemia by its tendency to regress spontaneously in a few weeks of life.[1] It is clinically characterized by asymptomatic organomegaly to bleeds, skin rash, hepatosplenomegaly, pericardial and pleural effusions leading to respiratory distress, progressive liver fibrosis, or fetal hydrops, in the most severe form.[4]

Association of TMD with DS is strikingly well-known. Around 4 to 10% of babies with DS develop TMD and 65% of them regress with/without treatment; however, 20 to 30% carry the risk of evolving later into AML-M7, usually within the first 4 years of life.[5]

Trisomy-21, either constitutional or mosaic, or even limited to the hematopoietic compartment, as in our patient, has been reported universally in TMD.[2] Trisomy-21 mosaicism has been described in 7 to 16% of cases of TMD. The risk of developing TMD or subsequent leukemia and the prognosis was not different in those with overt DS and mosaic DS. Trisomy-21 mosaicism remains a relevant diagnostic consideration in individuals with TMD, even in the absence of recognizable features of DS. Constitutional mosaicism can be difficult to prove, especially in the setting of hematopoietic abnormalities; therefore, further testing is warranted in this patient population.[2,6]

Pathogenesis of TMD is linked to the mutations in GATA-1 in X-chromosomes, most common being the exon-2 mutations. GATA-1 is vital in the normal erythropoiesis and megakaryopoiesis. Various other mutations have been described; however, all these lead to a truncated GATAs protein leading to TMD.[7,8]

Trisomy-21 remains the most common initial step in the leukemogenesis as the GATA-1 mutations per se do not lead to leukemia. GATA-1 mutation has a specific association with TMD and AML-M7, or AML-M7 of non-DS but with trisomy-21 within the leukemic blasts, and, it is not found in other cases of AML-M7 or other FAB types of AML, myelodysplastic syndromes, and acute lymphoblastic leukemia of patients with or without DS. Similar mutations in GATA-1 in cells without trisomy-21 have been shown to lead to anemia/neutropenia, but not leukemia.[9]

There are reports of neonates with TMD without other clinical features of DS who had mosaic trisomy-21 in blood and bone marrow at diagnosis.[10] In some of these reports, the mosaicism persisted after the TMD had resolved, but in others, once the TMD had resolved, trisomy-21 could not be identified in the blood.[10] Bertrums et al[11] reported a neonate at 12 days of age with features of TMD without trisomy-21 and GATA mutations with normal karyotyping, with a further detailed analysis showing cryptic deletions in 5q and 8q in blasts. The child after a spontaneous resolution had a frank AML-M7 relapse at 11 months of age with additional trisomy-6 and trisomy-19 and LOH (Loss of Heterozygosity) of chromosome 5 and was salvaged with chemotherapy.[12]

In patients with non-M7-non-DS TMD, flow cytometry revealed the same pattern as in TMD in DS patients. Majority of the cases in the non-DS cohort expressed CD33 and CD34[3]; recurrent cytogenetic abnormalities like t (8;16), trisomy-12 with GATA1 mutation, del (8) (q23.q24), del(5q) and del (13) (q13; q31), as well as germline THPO mutations and del (13) (q12.11) aberrations have been described.[13]

Tsai et al described two neonates with TMD without DS. These two patients showed trisomy-21 confined to the leukemic clone, similar to the index child; in addition, mutations within exon 2 of GATA1 were detected.[7] GATA mutation analysis could not be done in our patient due to logistic reasons. It is generally considered that trisomic cells may have a proliferative advantage over normal cells and as a consequence inhibit their growth. But they gradually lose this advantage and then cells with a normal karyotype dominate.[14]

A review of 16 patients with TMD without DS reported cytogenetical abnormalities in the blasts population involving chromosomes 21, in particular a gain of chromosome 21 (+21), clearly stating the role of trisomy-21 along with GATA mutation in TMD even in non-DS children.[1] Complications including hydrops and liver failure were not reported in non-DS children and hence a possibility that bone marrow might be the origin of TMD blasts in non-DS children, unlike in DS children, which usually involves the liver primarily.[1,4]

Although TMD can be fatal in 10% of patients, it often resolves spontaneously within 3 to 6 months without significant morbidity. Treatment is indicated in 15 to 20% of cases for complications including hyperleukocytosis (WBC >100,000 cells/mm^3), severe cytopenias, hydrops/effusions, respiratory distress, and liver dysfunction. Low-dose cytarabine for 5 to 10 days is the recommended regimen.[9] Tumor lysis syndrome is rarely reported after initiation of effective chemotherapy.[15]

Overall, children with DS are at a 500-fold excess risk of developing myeloid leukemia (ML-DS).[16] Individuals with a history of TMD have a 20 to 30% risk of developing ML-DS by 4 years and require close monitoring.[17] The natural history of TMD in DS is well known with monitoring suggestions for subsequent AML-M7; however, TMD in non-DS remains less explained in terms of pathogenesis and natural course.[17] However, reports of acute leukemia in non-DS TMD have been described as well.

Detailed cytogenetic analysis and the role of other pathogenic mutations contributing to TMD apart from trisomy-21 have to be studied. Bone marrow evaluation was not done in our patient as the diagnosis was established from peripheral blood for flow cytometry and cytogenetics. GATA-1 mutation analysis could not be done due to logistic reasons as mentioned.

Conclusion

TMD being a rare disorder with spontaneous remission in the majority is most often associated with DS children. Thorough evaluation for constitutional or mosaic DS is warranted in children with TMD. However, the knowledge that TMD with trisomy-21 is restricted to only leukemic clones helps in appropriate counseling/management and needs further insights into molecular mechanisms.

Disclosures

- The authors have no relevant financial or nonfinancial interests to disclose.
- The authors have no competing interests to declare that are relevant to the content of this article.
- All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.
- There are no prior publications or submissions with any overlapping information, including studies and patients.

Declaration of Patient Consent

Appropriate informed consent from parents of the child has been obtained.

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Conflicts of Interest

None declared.

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