

# A down syndrome patient diagnosed with transient myeloproliferative disease after presenting with cutaneous findings

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## Abstract

Transient myeloproliferative disease (TMD) is among the main hematologic problems seen in neonates with Down syndrome (DS). It is usually self-limiting and results in spontaneous remission within 3 to 6 months. Characteristic signs of TMD are leukocytosis, thrombocytopenia, anemia, hepatosplenomegaly, cutaneous nodules, and increased numbers of circulating blasts. In this article, we present a DS neonate without leukocytosis who was diagnosed as having TMD after a diffuse vesiculopapular eruption on the face, which is a different clinical presentation than other cases in the literature. Our aim is to emphasize the importance of early diagnosis and close multidisciplinary monitoring of these patients.

**Keywords:** Down syndrome; neonatal; transient myeloproliferative disease

## INTRODUCTION

Children with Down syndrome (DS) are at high risk for hematologic disorders such as benign leukemoid reaction and malignancy. Between 5% and 30% of children with DS are born with transient myeloproliferative disease (TMD), also known as transient abnormal myelopoiesis, which is characterized by clonal damage of megakaryoblasts and dysplastic changes in circulating cells (1-3). TMD associated with trisomy 21 is characterized by insertions, deletions, or point mutations in exons 2 and 3 of the *GATA1* gene, which encodes hematopoietic transcription factors.

Some patients with DS-TMD are asymptomatic, while others present with symptoms that require treatment, such as hyperviscosity, respiratory distress, hydrops fetalis, liver and kidney dysfunction, and congestive heart failure (4). Cutaneous symptoms are seen in only 5% of DS-TMD patients. In neonates, cutaneous findings typically manifest in the facial region as crusted papules, papulovesicles, and pustules on a diffuse erythematous base (5).

Many cases of DS-TMD resolve spontaneously without the need for treatment; 15–23% of patients die early, while

20–23% develops acute myeloid leukemia (AML) within the first 4 years. Overall, survival in DS-TMD is around 63–68% (4,6,7). Studies on this subject showed that in most patients (>80%), the clinical and laboratory findings of TMD spontaneously regressed within 3 to 6 months after birth (8).

In this article, we describe a neonate who was diagnosed as having TMD after developing diffuse vesiculopapular eruption on the face, a different clinical presentation than other cases in the literature.

## CASE REPORT

A baby boy weighing 2430 g was born at 37 weeks' gestation to a healthy 17-year-old mother by normal vaginal delivery after an unfollowed pregnancy. The baby had Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. After birth, the baby was admitted to the neonatal intensive care unit (NICU) due to grunting, nasal flaring, and tachypnea. Family history revealed no parental consanguinity, chronic diseases, and no use of medication by the mother. On physical examination, the infant had a body weight of 2430 g (10–25<sup>th</sup> percentile [p]), head circumference of 34 cm (50–75<sup>th</sup> p); pathologically,

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characteristic features of Down syndrome (hypertelorism, upward slanting palpebral fissures, depressed nasal bridge, short and thick neck, bilateral simian palmar crease, bilateral fifth finger clinodactyly, bilateral gap between the first and second toes) and grade 1/6 systolic murmur were detected. Other systemic and dermatologic examination findings were considered normal. In complete blood count analysis at admission, white blood cell (WBC) count was 28000/mm<sup>3</sup>, hemoglobin level was 19 g/dL, hematocrit was 56.2%, platelet count was 139000/mm<sup>3</sup>, and peripheral smear yielded no pathologic findings. The patient received noninvasive mechanical ventilation for 3 days due to respiratory distress, after which oxygen support was tapered and discontinued. Echocardiography performed due to worsening of the murmur during follow-up revealed complete atrioventricular septal defect. No pathology was detected in cranial and abdominal ultrasonography. Chromosome analysis revealed trisomy 21. On postnatal day 6, the baby developed numerous crusted papular lesions on the cheeks and periorbital area of the face, one on the right upper extremity, and one on the anterior torso. The lesions were bright red in color, erythematous, and some had a necrotic center; those on the cheeks showed a linear configuration (Figure 1A). Upon reanalysis of complete blood count due to the rash, WBC count was 32000/mm<sup>3</sup>, hemoglobin level was 15.4 g/dL, hematocrit was 48%, platelet count was 272000/mm<sup>3</sup>, uric acid level was 4.1 mg/dl, aspartate transaminase (AST) was 28 U/L, alanine transaminase (ALT) was 18 U/L, total bilirubin was 11.8 mg/dl, direct bilirubin was 1.1 mg/dl, and C-reactive protein level was 3.18 mg/L. Interleukin 6 level, body fluid and lesion swab cultures, and viral serologic tests of cerebrospinal fluid and serum samples for congenital infections (toxoplasmosis, syphilis, varicella-zoster virus (VZV), rubella, cytomegalovirus, and herpes simplex virus (HSV)) were negative. On postnatal day 14, the skin lesions had worsened, presenting as convergent, honey-colored crusted impetiginous papules with erythematous borders on the face, clusters of yellowish pink papules with erythematous edema on the arm extensor surface and clusters of bright red erythematous papules with central erosion in the lower quadrant of the abdomen (Figure 1B). Histological and immunohistochemical findings from a skin lesion biopsy performed during this period revealed atypical myeloid cell infiltration in the dermis, especially surrounding blood vessels (Figure 2A). On subsequent repeated peripheral smear, cell distribution was 16% large myeloblastic cells with basophilic cytoplasm, no granules in the cytoplasm, and occasional cytoplasmic blebbing, 52% lymphocytes, 20% neutrophils, 8% monocytes, 2% band cells, and 2% basophils and target cells. Flow cytometry of a peripheral blood sample was consistent with myeloid activity (CD7,CD33,CD34,CD36,CD38,CD41 and CD117 were positive). Bone marrow aspirate evaluation revealed 13% blasts, 41% lymphocytes, 25% neutrophils, 16% monocytes, 3% metamyelocytes, and 2% myelocytes, consistent with myeloproliferative disease (Figure 2B). No *GATA1* mutation was detected in molecular genetic analysis of peripheral blood performed for diagnostic confirmation of DS-TMD.

On postnatal day 28, after topical mupirocin therapy, a pale, red-brown patch (postlesional hyperpigmentation) was observed where the lesions were (Figure 3). The patient was discharged on postnatal day 30. He remains under follow-up in our pediatric cardiology and hematology outpatient clinic with no further complications. The family was referred for genetic counseling for future pregnancies.



Figure 1. A: Initial skin lesions; B: Before treatment, skin lesions

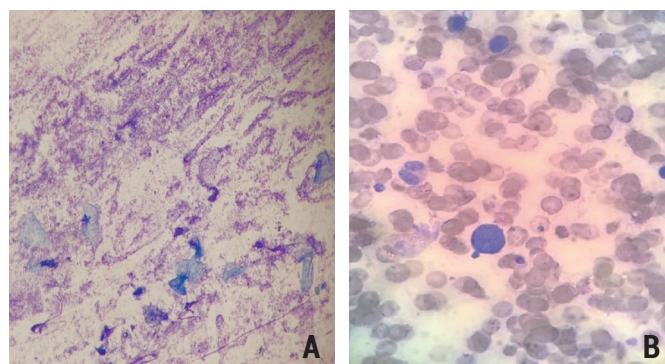


Figure 2. A: Skin Biopsy Histopathological View; B: Bone-Marrow Aspiration-Biopsy Histopathological View



Figure 3. After treatment, skin lesions

## DISCUSSION

Of the patients with DS-TMD, 10-25 % are asymptomatic while others present with symptoms that require treatment; such as hydrops fetalis, hyperviscosity, massive hepatosplenomegaly, pleural or pericardial effusion, respiratory distress, multiorgan failure, and

congestive heart failure (4). There are also some cases who presented with rare gastrointestinal symptoms (9). In the first few days after birth, our patient had respiratory problems due to transient tachypnea of the newborn, and the symptoms resolved during follow-up. Contrary to the usual clinical picture described in the literature, the presenting symptom in our patient was very rare which was skin lesions.

Cutaneous symptoms are seen in only 5% of patients with DS-TMD. In neonates, cutaneous manifestations usually appear on the face as crusted papules, papulovesicles, and pustules on a diffuse erythematous base (5). As seen in Figure 1A, our patient's cutaneous findings were comparable to those described in the literature. The differential diagnosis of the characteristic skin rash in TMD includes Langerhans cell histiocytosis, staphylococcal or streptococcal impetigo, HSV, VZV, erythema toxicum, and cutaneous candidiasis (5). Our patient's septic screening and viral serological tests of cerebrospinal fluid and serum samples obtained for congenital infections were negative.

TMD diagnosis can be made based on clinical signs, flow cytometry, and bone marrow examination (morphological and immunophenotypic findings according to megakaryocytic origin). Histologic findings in dermal samples (immature myeloid cells; atypical cells with epidermal exocytosis) may also assist in the diagnosis of TMD (10,11). In our case, flow cytometry examination of peripheral blood suggested myeloid activity and bone marrow biopsy evaluation was consistent with the diagnosis of myeloproliferative disease. Skin biopsy revealed atypical myeloid cell infiltration.

Nearly all patients with DS-TMD have mutations in the *GATA1* gene on the X chromosome, which encodes a transcription factor necessary for the maturation of megakaryocytes and erythroid cells. Because *GATA1* induces megakaryoblast proliferation in fetal hematopoiesis, this condition (usually) resolves upon the termination of fetal hematopoiesis at 3 months. Additional mutations are required for the development of overt leukemia in these patients (12). However, it has been emphasized in the literature that, patients with DS, hematologic involvement, and myeloid-derived blasts in peripheral smear should be regarded as having TMD until proven otherwise (13). Treatment is supportive unless the patient has life-threatening conditions such as multiorgan failure, respiratory distress, heart failure, and disseminated intravascular coagulation. *GATA1* mutation was not detected in the molecular genetic analysis of peripheral blood to confirm the diagnosis of DS-TMD in our case, but the findings detected in bone marrow, flow cytometry, and skin biopsy were considered sufficient for diagnosis.

## CONCLUSION

In this article, we report the case of a neonatal patient who presented in the early postnatal period with diffuse vesiculopapular eruption in the face and was subsequently

diagnosed with TMD. This clinical presentation is distinct from those described in the literature and demonstrates the importance of close, multidisciplinary monitoring of skin lesions in DS patients for early diagnosis. These patients should also be monitored regularly for conversion to overt leukemia.

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