Series Editor: Camila K. Janniger, MD

Vesiculopustular Eruption Associated With Transient Myeloproliferative Disorder

Erika Nornhold, MD; Anna Li, BS; Ilene L. Rothman, MD; Satyan Lakshminrusimha, MD; Thomas N. Helm, MD

Transient myeloproliferative disorder (TMD) is a hematologic abnormality usually associated with Down syndrome that may present with a skin eruption in addition to typical systemic findings. We report a case of a patient with TMD and a vesiculopustular eruption without the phenotypic characteristics of Down syndrome who was found to have mosaic trisomy 21. Mutations of the globin transcription factor 1 gene, GATA1, *are associated with both TMD and acute megakaryocytic leukemia. Transient myeloproliferative disorder typically presents with pancytopenia, hepatosplenomegaly, and immature circulating white blood cells, and affects approximately 10% of neonates with Down syndrome. These abnormalities rapidly regress within the first few months of life. However, 20% to 30% of neonates with Down syndrome and TMD later develop leukemia. The tumor antigen PRAME (preferentially expressed antigen in melanoma) may serve as a marker for leukemic transformation. We report an illustrative case to alert clinicians about this uncommon cause of vesiculopustular eruption in a neonate without the phenotypic characteristics of Down syndrome and review the clinical findings and laboratory studies that aid in accurate diagnosis.*

Cutis. 2009;83:234-236.

Case Report

The dermatology department was consulted for evaluation of a female neonate (day 3 of life) with an erythematous vesiculopustular eruption on the face, trunk, and extremities (Figure 1). She was born to a healthy primigravida woman at 40 weeks' gestation after an uncomplicated singleton pregnancy. Delivery was complicated by meconium-stained amniotic fluid. Clinical examination in the delivery room was remarkable for symmetric intrauterine growth restriction (birth weight, 2419 g [<2nd percentile]) and hepatosplenomegaly, but no dysmorphic physical features were noted. Initial hematologic workup revealed leukocytosis (89.6×10^9/L; reference range, $9.1–34.3\times10^9$/L) with 24% myeloblasts, thrombocytosis (1101×10^9/L; reference range, $150–450\times10^9$/L), and profound coagulopathy (prothrombin time, 28.1 seconds [reference range, 10–15 seconds]; partial thromboplastin time, 65.5 seconds [reference range, 23–35 seconds]; fibrinogen, <60 mg/dL [reference range, 200–470 mg/dL]). The patient was admitted to the neonatal intensive care unit with concerns of sepsis in the setting of immunosuppression and was started on ampicillin sodium, gentamicin sulfate, and acyclovir sodium after bacterial and viral cultures were obtained. Aside from an infectious etiology, the initial differential diagnosis included transient neonatal pustular melanosis, erythema toxicum neonatorum, Langerhans cell histiocytosis, leukemia cutis, and eosinophilic pustular folliculitis. Cultures were negative for bacterial and viral infection, and the clinical course did not support the entities considered in the differential diagnosis. A possible diagnosis of transient myeloproliferative disorder (TMD) was suggested on consultation with the hematology department. Karyotype analysis was ordered to look for possible mosaic Down syndrome.

Examination of the patient's skin revealed erythematous papules with yellow crusts as well as pustules on the face, trunk, and extremities that worsened over the following few days. A punch biopsy specimen of the skin taken on day 3 of life

Accepted for publication December 18, 2008.

Drs. Nornhold, Rothman, and Helm, and Ms. Li are from the Department of Dermatology and Dr. Lakshminrusimha is from the Department of Pediatrics, all from University at Buffalo, The State University of New York.

The authors report no conflict of interest.

Correspondence: Erika Nornhold, MD, SUNY-Buffalo, 1036 Lakeview Terr #B, Grand Island, NY 14072 (erikadowns@hotmail.com).

Figure 1. A female neonate with an erythematous vesiculopustular eruption on the face associated with transient myeloproliferative disorder (A). Vesicles and pustules also were present on the trunk and extremities (B).

revealed serous crust; necrosis of the epidermis; and a mixed inflammatory infiltrate of neutrophils, lymphocytes, histiocytes, and eosinophils. Immature myeloid cells also were noted (Figure 2). The histologic findings supported the clinical impression of TMD. Flow cytometry of the peripheral blood revealed numerous $CD56^+$ white blood cells and karyotype analysis revealed mos 46,XX/47,XX,+21.

The patient's leukocytosis and thrombocytosis improved over the first week of life, but liver function progressively worsened. The patient was treated with a 7-day course of cytosine arabinoside and the skin lesions dramatically improved as liver dysfunction gradually resolved. She was discharged home at 4 weeks of age.

Comment

Transient myeloproliferative disorder is somewhat of a mystery because the abnormal proliferation of cells, in many cases, spontaneously resolves for unknown reasons.[1] Approximately 10% of neonates with Down syndrome develop TMD. However, in patients without phenotypic characteristics of Down syndrome, as in our patient, the disorder can manifest in the setting of trisomy 21 mosaicism.[2] Mosaicism refers to the presence of 2 or more genetically distinct cell populations in a single individual.[3]

Most cases of TMD and acute megakaryocytic leukemia in children involve mutations of the globin transcription factor 1 gene, *GATA1*.[4] Genetic abnormalities typically result in the exclusive production of a short *GATA1* isoform, *GATA1s*. Abnormal

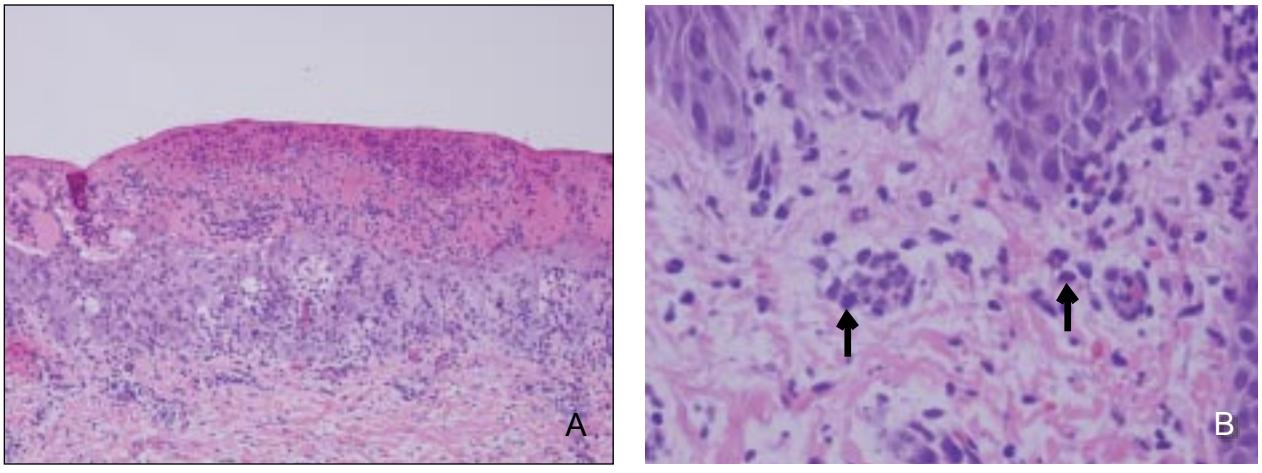

Figure 2. Examination of a punch biopsy specimen reveals necrosis of the epidermis and a mixed inflammatory infiltrate (A)(H&E, original magnification ×40). High magnification reveals neutrophils, lymphocytes, histiocytes, eosinophils, and immature myeloid cells (arrows)(B)(H&E, original magnification ×80).

GATA1 has a pronounced effect on liver progenitor cells and individuals with Down syndrome have up to a 20-fold increased risk for developing leukemia. In addition to a *GATA1* mutation, a still unidentified genetic factor is thought to be involved in the evolution of leukemia.[4] Multiple separate *GATA1* mutant clones can occur in the same patient with Down syndrome, but identical *GATA1* mutations also have been noted in the myleoblasts of patients with TMD. The myleoblasts of TMD are sensitive to low-dose cytosine arabinoside.[5] Typical peripheral blood findings include leukocytosis with neutrophils within reference range and up to one-fourth of cases may be asymptomatic.[4] The number of myeloblasts may represent up to 90% of circulating nucleated cells. Bone marrow biopsy findings are variable and often are not helpful because they may reveal megakaryocyte counts that are increased, decreased, or within reference range. The tumor antigen PRAME (preferentially expressed antigen in melanoma) may be a specific marker for acute megakaryocytic leukemia blasts, with no expression in TMD. These findings may prove to be particularly helpful because the myeloblasts seen in TMD and acute megakaryocytic leukemia are morphologically identical on routine microscopy and can have the same acquired mutations in *GATA1*.[7]

Our patient needs close hematologic follow-up. It is not yet clear if there is a similar likelihood of developing leukemia in individuals with mosaic Down syndrome and classic trisomy 21. Furthermore, not enough cases of TMD-associated skin eruptions have been reported to determine if the type of Down syndrome could be a marker for either increased or decreased risk for leukemia.

REFERENCES

1. Rhoderick JA, Bradshaw WT. Transient myeloproliferative disorder in a newborn with Down syndrome. *Adv Neonatal Care*. 2008;8:208-218.
2. Magalhães IQ, Splendore A, Emerenciano M, et al. Transient neonatal myeloproliferative disorder without Down syndrome and detection of *GATA1* mutation. *J Pediatr Hematol Oncol*. 2005;27:50-52.
3. James WD, Berger TG, Elston DM, eds. *Andrews' Diseases of the Skin: Clinical Dermatology*. 10th ed. New York, NY: Saunders Elsevier; 2006.
4. Vyas P, Crispino JD. Molecular insights into Down syndrome–associated leukemia. *Curr Opinion Pediatr*. 2007;19:9-14.
5. Brink DS. Transient leukemia (transient myeloproliferative disorder, transient abnormal myelopoiesis) of Down syndrome. *Adv Anat Pathol*. 2006;13:256-262.
6. Hanna MD, Melvin SL, Dow LW, et al. Transient myeloproliferative syndrome in a phenotypically normal infant. *Am J Pediatr Hematol Oncol*. 1985;7:79-81.
7. McElwaine S, Mulligan C, Groet J, et al. Microarray transcript profiling distinguishes the transient from the acute type of megakaryoblastic leukaemia (M7) in Down's syndrome, revealing PRAME as a specific discriminating marker. *Br J Haematol*. 2004;125:729-742.