Series Editor: Camila K. Janniger, MD

Vesiculopustular Eruption in a Neonate With Trisomy 21 Syndrome as a Clue of Transient Myeloproliferative Disorders

Fiammetta Piersigilli, MD; Andrea Diociaiuti, MD; Renata Boldrini, MD; Cinzia Auriti, MD; Marco Curci, MD; Maya El Hachem, MD; Giulio Seganti, MD

We report the case of a vesiculopustular eruption associated with a transient myeloproliferative disorder (TMD) in a neonate with trisomy 21 syndrome. Examination of a skin biopsy showed a dermal mixed inflammatory infiltrate including atypical megakaryoblasts. As the white blood cell count spontaneously normalized, the eruption disappeared. This case report and review of the literature demonstrates that a vesiculopustular eruption could be an important clue to identify TMD in a neonate.

Cutis. 2010;85:286-288.

Neonates with trisomy 21 syndrome are at increased risk for the development of leukemoid reactions, transient myeloproliferative disorders (TMDs), and congenital leukemia. A leukemoid reaction is an acute form of leukocytosis with a white blood cell count exceeding 50.0×10^9/L (reference range, 4.5–11.0×10^9/L) that is secondary to underlying stress on the bone marrow (ie, infections, hemolysis, prenatal corticosteroids). It is completely reversible upon removal of the stimulus.[1] A TMD is a self-limiting form of acute myelocytic leukemia with increased blast cells in the bone marrow and peripheral blood as well as hepatosplenomegaly. Transient myeloproliferative disorders manifest almost exclusively in neonates with trisomy 21 syndrome, though some reports describe it in neonates who, despite being phenotypically normal, are mosaic for trisomy 21 syndrome.[2-4] Between 20% and 30% of infants with TMD eventually have a leukemia relapse, usually within a few years after resolution of TMD and most frequently acute megakaryoblastic leukemia.[5]

Leukemia cutis is found in approximately 25% to 30% of all neonates with congenital leukemia.[6] The typical skin lesions are blue or violaceous nodules measuring approximately 1 to 2 cm in diameter, sometimes accompanied by ecchymoses. Histologic examination reveals a dermal infiltrate of leukemic cells. Leukemoid reactions and TMDs also can be associated with various cutaneous manifestations such as vesiculopustular eruptions[7] that spontaneously resolve without treatment. The development of pustules in a neonate requires a differential diagnosis to exclude numerous conditions, such as infectious diseases, other transient neonatal pustulosis, incontinentia pigmenti, and Langerhans cell histiocytosis.[8] We report the case of a neonate with trisomy 21 syndrome who presented with a vesiculopustular eruption associated with a TMD that spontaneously disappeared without treatment.

Case Report

An 8-day-old neonate with trisomy 21 syndrome was referred to the Department of Neonatology for investigation of a vesicular eruption on the left arm. She was born at 38 weeks' gestation to a 41-year-old mother (gravida 4, para 3, aborta 1). The mother had no history of herpes simplex virus infection, varicella, or febrile illness during pregnancy. Human immunodeficiency virus serology was negative. Amniocentesis led to a prenatal diagnosis of trisomy 21 sydrome. Delivery was spontaneous and without complications. The neonate was kept under observation for 5 days before discharge from the nursery.

Drs. Piersigilli, Auriti, and Seganti are from the Department of Neonatology; Drs. Diociaiuti and El Hachem are from the Department of Dermatology; and Dr. Boldrini is from the Department of Pathology, all from the Bambino Gesù Children's Hospital, Rome, Italy. Dr. Curci is in private practice, Modena, Italy.
The authors report no conflict of interest.
Correspondence: Andrea Diociaiuti, MD, Department of Dermatology, Bambino Gesù Children's Hospital, Piazza S Onofrio 4 00165 Rome, Italy (diociaiuti@opbg.net).

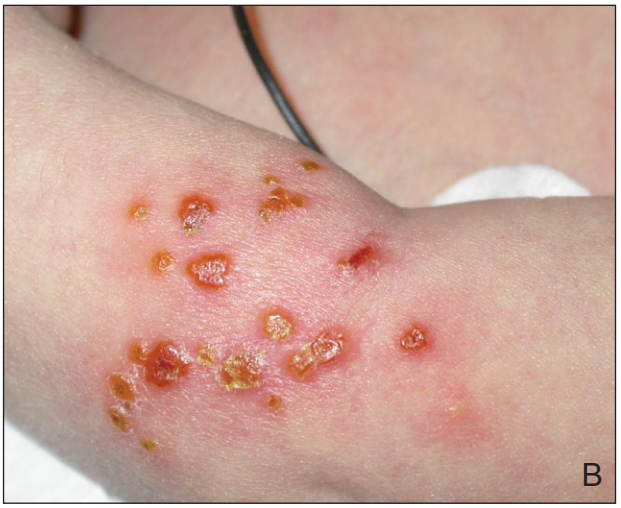

Figure 1. Vesiculopustular eruption on the face (A) and left arm (B).

On admission, the neonate was afebrile and had normal findings from a general physical examination. Routine laboratory tests showed an elevated white blood cell count at 65.2×10^9/L. The elevated white blood cell count persisted, and therapy was started the next day (day 10 of life) with amoxicillin and topical aqueous solution of eosin 2%. The papular eruption worsened and the neonate developed numerous, grouped, papulovesicular and papulopustular lesions with underlying erythema as well as some yellowish crusts on the cheeks, eyelids, and arms (Figure 1); there was no lymphadenopathy. Abdominal examination showed an enlarged liver and spleen; the liver edge was palpable 2 cm below the right costal margin, and the splenic tip was palpable 1 cm from the left costal margin. On day 12, routine laboratory tests still showed a persistently elevated white blood cell count (66.9×10^9/L) with 70% blasts and an elevated lactate dehydrogenase concentration at 1780 U/L (reference range, 100–200 U/L). Blood and urine cultures and swabs from the skin lesions detected no bacterial infection. Tzanck test results were negative and polymerase chain reaction analysis was negative for herpes viruses. The neonate had normal neurologic examination findings, and she was feeding well and afebrile.

Bone marrow aspiration revealed increased white blood cells and myeloblasts with nuclear atypia suggestive of a TMD or acute myelocytic leukemia. Histologic evaluation of a punch biopsy specimen showed a mildly acanthotic epidermis that was focally eroded. Within the superficial dermis and extending into the epidermis were large mononuclear cells with hyperchromatic nuclei and abundant eosinophilic cytoplasm consistent with immature myeloid cells (Figure 2). Immunohistochemical stains showed strong immunoreactivity of these cells with myeloperoxidase and a megakaryocytic cell marker LAT (linker for activation of T cells), confirming that the cells were of myeloid and megakaryoblastic origin. The histologic findings supported the clinical suspicion of a TMD.

The white blood cell count remained elevated but stable and the hepatosplenomegaly did not worsen; further treatment was not initiated. After 8 weeks, the white blood cell count normalized, and as the TMD resolved, the skin lesions disappeared. The 18-month-old infant is well and manifests no signs of hematologic alterations.

Comment

The differential diagnosis of a neonatal vesiculopustular eruption is broad and includes infectious, reactive, and neoplastic conditions. In patients with trisomy 21 syndrome, a leukemoid reaction, TMD, and congenital leukemia also should be considered. Congenital leukemia could necessitate chemotherapy in particular conditions when the malignancy interferes with vital parameters, but postponement of chemotherapy in these frail neonates will result in less toxicity and probably a better survival, especially for patients with trisomy 21 syndrome.[9]

In our patient, after an infection was ruled out, the bone marrow biopsy confirmed a myeloproliferative disorder and the patient demonstrated the cutaneous pustular lesions described as an expression of leukemic infiltrates.[3,6,10,11] The neonate's good general clinical condition, with only an elevated white blood cell count and no problem of increased viscosity as well as mild hepatosplenomegaly, allowed more conservative treatment, and spontaneous resolution was consistent with the diagnosis of TMD.

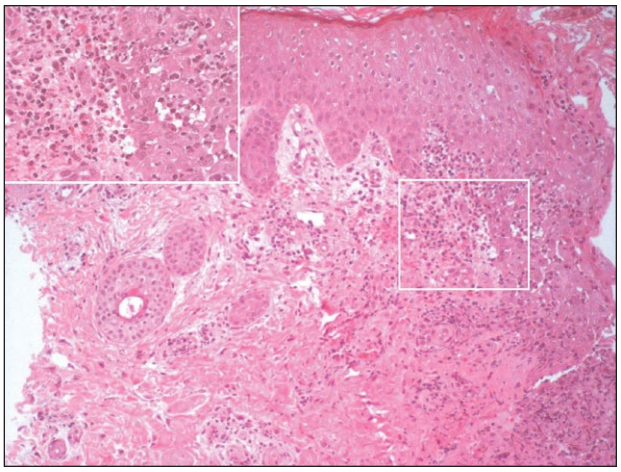

Figure 2. An acanthotic epidermis that was focally eroded. Large mononuclear cells with hyperchromatic nuclei and abundant eosinophilic cytoplasm were seen in the superficial dermis and extending into the epidermis (H&E, original magnification ×10). The insert shows in better detail the morphology and location of the myeloid cells (H&E, original magnification ×40).

This case report is instructive for clinical practice because it confirms prior reports of the association of a pustular rash in a neonate with trisomy 21 syndrome and a TMD; very few cases of TMD presenting with vesicopustules have been described in the literature.[11] The lesions predominantly appeared on the face, especially concentrated in areas where pressure had been applied; 2 patients died of acute megakaryoblastic leukemia.[12,13]

Although TMDs are benign conditions, the neonate should undergo strict follow-up once the elevated white blood cell count returns to within reference range because of the risk for leukemia later in life.[12] Currently, t(7;11)(p15;p15) at the time of the TMD is the only prognostic feature associated with subsequent leukemia.[13] Mutations of the globin transcription factor 1 gene, *GATA1*, have been identified in a large percentage of cases of TMD and persistently up-regulated expression of the Wilms tumor 1 gene, *WT1*, is postulated to be associated with an elevated risk for subsequent development of acute megakaryoblastic leukemia.[14-17] These caveats hold true even in a phenotypically normal neonate because a TMD also has been described in normal neonates who are mosaic for trisomy 21 syndrome.[2,4]

REFERENCES

1. Cohen A, Barak M, Herschkowitz S, et al. Leukemoid reaction induced by prenatal administration of betamethasone. *Acta Pediatr Jpn*. 1993;35:534-536.
2. Seibel NL, Sommer A, Miser J. Transient neonatal leukemoid reactions in mosaic trisomy 21. *J Pediatr*. 1984;104:251-254.
3. Solky BA, Yang FC, Xu X, et al. Transient myeloproliferative disorder causing a vesiculopustular eruption in a phenotypically normal neonate. *Pediatr Dermatol*. 2004;21:551-554.
4. Lerner LH, Wiss K, Gellis S, et al. An unusual pustular eruption in an infant with Down syndrome and a congenital leukemoid reaction. *J Am Acad Dermatol*. 1996;35 (2, pt 2):330-333.
5. Zipursky A, Brown E, Christensen H, et al. Leukemia and/or myeloproliferative syndrome in neonates with Down syndrome. *Semin Perinatol*. 1997;21:97-101.
6. Resnik KS, Brod BB. Leukemia cutis in congenital leukemia. analysis and review of the world literature with report of an additional case. *Arch Dermatol*. 1993;129: 1301-1306.
7. Nijhawan A, Baselga E, Gonzalez-Ensenat MA, et al. Vesiculopustular eruptions in Down syndrome neonates with myeloproliferative disorders. *Arch Dermatol*. 2001;137:760-763.
8. Mengesha YM, Bennett ML. Pustular skin disorders: diagnosis and treatment. *Am J Clin Dermatol*. 2002;3:389-400.
9. van den Berg H, Hopmann AH, Kraakman KC, et al. Spontaneous remission in congenital leukemia is not related to (mosaic) trisomy 21: case presentation and literature review. *Pediatr Hematol Oncol*. 2004;21:135-144.
10. Burch JM, Weston WL, Rogers M, et al. Cutaneous pustular leukemoid reactions in trisomy 21. *Pediatr Dermatol*. 2003;20:232-237.
11. Su WP. Clinical, histopathologic, and immunohistochemical correlations in leukemia cutis. *Semin Dermatol*. 1994;13:223-230.
12. Viros A, Garcia-Patos V, Aparicio G, et al. Sterile neonatal pustulosis associated with transient myeloproliferative disorder in twins. *Arch Dermatol*. 2005;141:1053-1054.
13. Wirges ML, Stetson CL, Oliver JW. Pustular leukemoid reaction in a neonate with Down syndrome. *J Am Acad Dermatol*. 2006;54(suppl 2):S62-S64.
14. Dixon N, Kishnani PS, Zimmerman S. Clinical manifestations of hematologic and oncologic disorders in patients with Down syndrome. *Am J Med Genet C Semin Med Genet*. 2006;142:149-157.
15. Wechsler J, Greene M, McDevitt MA, et al. Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. *Nat Genet*. 2002;32:148-152.
16. Mundschau G, Gurbuxani S, Gamis AS, et al. Mutagenesis of GATA1 is an initiating event in Down syndrome leukemogenesis. *Blood*. 2003;101:4298-4300.
17. Hasle H, Lund B, Nyvold CG, et al. WT1 gene expression in children with Down syndrome and transient myeloproliferative disorder. *Leuk Res*. 2006;30:543-546.