Vesiculopustular Eruptions in Down Syndrome Neonates With Myeloproliferative Disorders

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Background: Infants with Down syndrome are at increased risk for hematologic abnormalities, including leukemoid reaction, transient myeloproliferative disorder, and congenital leukemia. The differential diagnosis of a vesiculopustular eruption in an infant with Down syndrome and these hematologic abnormalities is broad and includes benign, self-limited disorders as well as life-threatening infections.

Observation: We describe 3 newborns with Down syndrome and vesiculopustular eruptions associated with myeloproliferative disorders during the neonatal period. These lesions differ from other neonatal vesicular eruptions in that they have a unique distribution, display pathergy, and contain immature hematopoietic cells similar to circulating blast cells. Resolution occurs without treatment as the hematologic disorder subsides.

Conclusions: Infants with Down syndrome and hematologic abnormalities may have a cutaneous eruption that has characteristic clinical and histopathologic findings. It is possible that this eruption has been unrecognized in the past because of its self-limited course. Whether this eruption is a prognostic factor for the subsequent development of leukemia is uncertain.

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The differential diagnosis for neonatal vesiculopustular eruptions includes infectious and noninfectious causes. We describe an unusual vesiculopustular eruption in 3 neonates with Down syndrome and hematologic abnormalities.

Infants with Down syndrome have an increased risk of hematologic abnormalities, including leukemoid reaction, transient myeloproliferative disorder, and congenital leukemia. A leukemoid reaction is a secondary overproduction of leukocytes in response to stimuli such as infection, hemolysis, or perinatal steroid administration.1 Transient myeloproliferative disorder differs from a leukemoid reaction in that there is no identifiable trigger. Both transient myeloproliferative disorder and congenital leukemia are characterized by increased blast cells in the bone marrow and peripheral blood and hepatosplenomegaly. Anemia and thrombocytopenia may or may not be present.2 Unlike transient myeloproliferative disorder, which is self-limited, congenital leukemia requires treatment to alter its course.

Leukemia cutis is most commonly associated with acute myelogenous leukemia and manifests as papules or nodules, which histologically correspond to a dermal leukemic infiltrate. Cutaneous manifestations of transient myeloproliferative disorder are not well described.

A vesiculopustular eruption containing immature myeloid cells has been documented in one infant with Down syndrome and a leukemoid reaction. This infant subsequently developed myelodysplasia at 1 year of age and acute myelogenous leukemia at 2 years of age.3 We report 3 additional cases of cutaneous infiltration of immature hematopoietic cells in patients with Down syndrome and myeloproliferative disorders.

REPORT OF CASES

CASE 1

A 13-day-old boy with Down syndrome was transferred to a neonatal intensive care unit because of persistent leukocytosis, generalized edema, hepatomegaly, cardiomegaly, and respiratory distress. The neonate was delivered by cesarean section to a 20-year-old, gravida 2, para 2, healthy mother at 36 weeks’ gestational age. Birth weight was 2970 g. Cytogenetic analysis

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of cells from peripheral blood revealed trisomy 21 with no other cytogenetic abnormalities. Shortly after birth, the patient was noted to have a white blood cell count of 106 × 10^9/L with blast cells on peripheral smear. The hematocrit and platelet count were normal. The white blood cell count peaked at 185 × 10^9/L on day 9 of life. Intravenous antibiotic therapy for suspected pneumonia was initiated.

On day 13 of life, he had persistent leukocytosis (white blood cell count of 153 × 10^9/L with 46% blast cells), hepatomegaly, and respiratory distress. Erythematous papules and pustules were noted on the neonate’s face where moisture-retentive dressing (Duoderm) had been placed. Despite treatment with mupirocin, the facial eruption persisted and similar lesions appeared at sites of trauma.

The dermatology department was consulted on day 24 of life. The neonate’s leukocytosis was resolving (white blood cell count of 32.5 × 10^9/L) and he was receiving supportive care. Physical examination revealed an intubated newborn with features of Down syndrome. There were multiple 1- to 3-mm, red, crusted papules, pustules, and vesicles on the cheeks and forehead, with similar papules and vesicles on the medial aspects of his arms and left leg corresponding to sites of previous needle sticks and intravenous catheters (Figure 1A-B). A Tzanck smear was negative. Wright-stained smears of fluid from the facial lesions revealed predominantly promyelocytes and myelocytes with rare myeloblasts (Figure 2). A skin biopsy specimen from a vesicle on the left leg revealed subcorneal spongiotic vesicles with immature myeloid infiltrate in the vesicles and in the perivascular superficial dermis (Figure 3A-B). Myeloid lineage was confirmed with immunohistochemical staining. The immature cells found in the peripheral smear, Wright-stained smear of the facial lesions, and the skin biopsy specimen were similar. Cultures of blood, skin, and bronchoalveolar lavage fluid failed to isolate bacte-
rial, viral, or fungal pathogens. A diagnosis of leukemoid reaction was presumed.

During subsequent weeks, the infant’s leukocytosis resolved and skin lesions healed without scarring. His respiratory status improved, and he was discharged at 2 months of age. He remains healthy at 4 months of age.

CASE 2

A neonate with Down syndrome and his phenotypically normal fraternal twin sister were born to a 34-year-old, healthy mother by cesarean section at 35 weeks’ gestational age. Birth weight of the infant with Down syndrome was 2030 g. Shortly after birth, the white blood cell count was 30.0 $\times 10^9$/L with 20% blast cells on peripheral smear. At 24 hours of life, the neonate developed skin lesions initially diagnosed as erythema toxicum by the primary care physician. The patient was transferred to a tertiary care hospital on day 7 with persistent leukocytosis (white blood cell count was 87.0 $\times 10^9$/L with 80% blast cells), lymphadenopathy, and splenomegaly. A bone marrow biopsy specimen revealed 76% blast cells. Immunohistochemical stains and cell surface markers were consistent with acute lymphoblastic leukemia. Karyotype of cells from the bone marrow biopsy specimen revealed trisomy 21. Skin examination revealed umbilicated vesicles, erythematous papules, and pustules on the face, trunk, and extremities. Lesions were also present on the palms and soles. A Tzanck smear and rapid herpes simplex virus test results were negative. Cytological analysis of pustular contents revealed immature leukocytes. The skin lesions crusted and healed during the next 7 days. No further skin lesions appeared.

Initially the neonate was treated for presumed myeloproliferative disorder with corticosteroids and allopurinol. Induction chemotherapy (daunoblastine, vincristine sulfate, methotrexate, cytarabine, cyclophosphamide, and asparaginase) for acute lymphocytic leukemia was given during weeks 3 to 12 of life. The infant was believed to be in remission and discharged at 3 months of age. He was readmitted at 6 months of age with septic shock. Blood cultures and cultures of an intravenous line grew *Staphylococcus epidermidis*. Despite antibiotic therapy, the patient died.

CASE 3

A 1850-g female neonate with Down syndrome was born to a 27-year-old, gravida 3, para 2, healthy mother by cesarean section at 31 weeks’ gestational age. Her prenatal course was complicated by fetal tachycardia, which was treated with digoxin. Ultrasound revealed a ventricular septal defect and an overriding aorta. Amniocentesis revealed trisomy 21. In anticipation of a premature delivery, the neonate’s mother received systemic steroids 1 week before cesarean section. Shortly after birth, the neonate was noted to have a white blood cell count of 13.6 $\times 10^9$/L with 42% blast cells in the peripheral blood. Sepsis workup included a lumbar puncture, which revealed 11% blast cells. Ultrasound of the head revealed periventricular calcifications. The dermatology department was consulted on day 2 of life for crusted vesiculopustular lesions on the cheeks and chin. Gram stain, bacterial culture, and rapid herpes simplex virus and varicella-zoster virus test results of the lesions were negative. A Wright-stained smear from an intact pustule on the neonate’s chest revealed immature myelocytes and promyelocytes with some mature neutrophils. The skin lesions resolved without treatment by 2 weeks of life as the hematologic findings normalized. She remains healthy at 7 months of age.

COMMENT

Leukocytosis in an infant can be a primary or secondary event. Primary causes include transient (transient myeloproliferative disorder) or persistent (congenital leukemia) dysregulation and proliferation of immature hematopoietic cells. Secondary leukocytoses include a leukemoid reaction, which has been defined as a total leukocyte count exceeding 50.0 $\times 10^9$/L. In a leukemoid reaction, the peripheral blood often has increased numbers of immature myeloid cells. This reaction has been
reported to occur in response to congenital infections, bacterial neonatal infections, hemolytic disorders, prenatal betamethasone, and malignant neoplasms such as neuroblastoma.\(^1\)\(^4\)\(^5\)

Infants with Down syndrome are at increased risk for both congenital leukemia and transient myeloproliferative disorder.\(^6\) Although most cases of transient myeloproliferative disorder have a sustained, spontaneous remission, 20% of affected patients ultimately develop acute leukemia later in life.\(^7\) There are no well-established prognostic features that predict which infants later develop leukemia, although it has been suggested that additional chromosome changes at the time of the myeloproliferative disorder may be associated with subsequent leukemia.\(^2\)

Our cases all involved premature infants with myeloproliferative disorders. Their vesiculopustular eruptions appeared within the first few days of life. The severity of the eruption varied. In case 1, the neonate had marked leukocytosis (peak white blood cell count of \(185 \times 10^9/L\)) with circulating blast cells and numerous coalescing lesions on the face and at sites of trauma (pathergy). In contrast, case 3 had only minimal leukocytosis with a similar percentage of circulating blast cells and only a few scattered pustules. In all 3 cases, the pustules contained immature myeloid cells demonstrable on Wright-stained preparations. The cells identified in the skin resembled those of the peripheral blood.

Although the hematologic findings of transient myeloproliferative disorders are well characterized, associated cutaneous findings are usually not mentioned. In contrast, cutaneous infiltrates of leukemic cells (leukemia cutis) are often associated with congenital leukemias.\(^8\) These lesions most commonly appear as blue, firm infiltrative papules and nodules that histologically correlate with a nodular or perivascular dermal infiltrate of leukemic cells.\(^9\) Vesiculopustular eruptions with superficial epidermal infiltrates are not described. Leukemia cutis differs both clinically and histologically from the pustules observed in our patients. We could identify only one report of an infant with Down syndrome who had a congenital “leukemoid reaction” and a pustular eruption containing immature myeloid cells.\(^3\)

Our cases were not consistent with classic descriptions of known neonatal pustular eruptions. Histologically, the lesions of impetigo, transient neonatal pustular melanosis, infantile acropustulosis, and Sweet syndrome reveal mature neutrophils. Sweet syndrome has been reported in infancy\(^10\) but is usually accompanied by fever, leukocytosis, and infiltrative erythematous plaques. In contrast to our cases, eosinophils are abundant in the vesicles of infants with erythema toxicum, eosinophilic folliculitis, and incontinentia pigmmenti. Bacterial, viral, and yeast (Candida) infections were unlikely in our cases since the gram stain, Tzanck smear, and cultures were negative. Although one of the infants was suspected to have congenital cytomegalovirus, this was not isolated from skin lesions.

The significance of this eruption is uncertain. A previously reported neonate with Down syndrome who displayed a similar eruption eventually developed acute myelogenous leukemia at the age of 2 years.\(^3\) One of our patients was diagnosed as having acute lymphoblastic leukemia at 2 weeks of age. Future studies will be required to determine if the leukemoid eruption described in this article is a harbinger of leukemia. Careful long-term follow-up of these infants seems warranted.

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REFERENCES