Series Editor: Camila K. Janniger, MD

Erythema Toxicum Neonatorum Revisited

Aaron J. Morgan, MD; Christopher J. Steen, MD; Robert A. Schwartz, MD, MPH; Camila K. Janniger, MD

Erythema toxicum neonatorum (ETN) is a common neonatal dermatologic disorder that usually is evident within the first 48 hours of life. Characteristic lesions include erythema, wheals, papules, and pustules. This transient rash resolves spontaneously without sequelae over the course of a week. Histologically, ETN shows an abundance of eosinophils. Although it has been recognized and described for centuries, the etiology and pathogenesis of ETN remain unclear.

Cutis. 2009;83:13-16.

Erythema toxicum neonatorum (ETN) has been recognized for centuries. Ancient Mesopotamian physicians attributed this rash to "nature's method of cleansing the child of the impure blood of the mother."[1] Bartholomaeus Metlinger, a 15th century pediatrician, is recognized as one of the first physicians to document the condition.[2] In 1752, the British physician William Smellie, theorized that what nurses referred to as "the red gum" in London, England, and "the hives" in Scotland was merely a reaction to meconium remaining on the neonate's skin.[3] Since then, it has been known as *erythema papulatum*[4]; *erythema dyspepsicum*[5]; *erythema neonatorum allergicum*[6,7]; *urticaria neonatorum*[8]; and ultimately ETN, a term coined by Carl Leiner in 1912.[9]

Epidemiology

Erythema toxicum neonatorum affects neonates of all races and ethnicities worldwide. The incidence is reported to range from as low as 3.7% to as high as 72%.[10,11] Results of a survey of 900 neonates in India demonstrated an incidence of 20.6%. In this study, ETN was ranked the sixth most common lesion of neonates after Epstein pearls (88.7%), mongolian spots (62.2%), milia (34.9%), sebaceous hyperplasia (31.8%), and salmon patches (28.4%), respectively.[12] Another evaluation of 620 healthy term infants sampled in Milan, Italy, reported an incidence of 23%. This study evaluated neonates only during the first 3 days of life and thus likely provided an underestimate of the actual incidence.[13] A 1986 study reported that 40.8% of 5387 Japanese neonates examined over 10 years were affected by ETN. In this evaluation, ETN was the most common dermatologic condition noted in neonates.[14] A study of the epidemiology of ETN examined 783 Chinese neonates and determined the incidence to be 43.7%.[15]

There appears to be no notable racial, ethnic, sexual, or seasonal predilection. However, some studies demonstrate higher incidence rates of ETN in males than females.[15,16] In 356 Spanish newborns, 25.3% had ETN (61.9% male and 38.1% female).[16] Therefore, if a sexual discrepancy exists in individuals affected by ETN, the margins appear to be small.

The only pivotal factors associated with an increased relative incidence of ETN are increased birth weight, size, and gestational age. Of 270 newborns examined in Los Angeles, California, the incidence of ETN increased from 0% to 55% as the birth weight increased from 1500 to 2500 g. This analysis also found that as the gestational age increased from 30 weeks or less to 42 weeks or more, the incidence increased from 0% to 59%.[17] Several studies have confirmed that higher incidence rates of ETN are seen in term infants and neonates weighing more than 2500 g compared to neonates of lower birth weight and gestational age.[12,14,15,17,18]

Etiology

The etiology of ETN remains the most elusive of its features. Erythema toxicum neonatorum has been known by many names reflecting numerous etiologic theories. In 1752, Smellie[3] believed that "the red gum" was due to meconium remaining on the skin of newborns because of insufficient cleansing. Interestingly, approximately 200 years later,

Accepted for publication December 12, 2007.

From Dermatology and Pediatrics, New Jersey Medical School, Newark.

The authors report no conflict of interest.

Correspondence: Camila K. Janniger, MD, Pediatric Dermatology, New Jersey Medical School, 185 South Orange Ave, Newark, NJ 07103 (janniger@yahoo.com).

Keitel and Yadav[19] postulated that "our preoccupation with cleanliness" and the vigorous removal of the vernix caseosa contribute to the development of dermatoses such as ETN. In 1912, Leiner[9] stated that what was termed *erythema dyspepsicum* by Moro[5] in 1910 may be a manifestation of the systemic absorption of enterotoxins in newborns with dyspepsia. Furthermore, in 1927, Mayerhofer and Lypolt-Krajnovic[6,7] compared erythema neonatorum allergicum to the allergic nature of serum sickness.

Because of the predominance of eosinophilic infiltrates in ETN, some believe allergy to be the underlying mechanism. Various possible allergens have been suggested, including vaginal secretions, infant formula, medications taken during pregnancy, and toxins both in utero and the environment, yet none have been substantiated. It has been determined that ETN is not affected by mode of feeding, medications, or method of skin care.[1] Erythema toxicum neonatorum present at birth has been cited as evidence suggesting that the condition develops independent of allergens in the environment.[20] Furthermore, a survey of relatives of neonates with ETN found no notable relationship between ETN and family history of atopy.[19] Thus, Keitel and Yadav[19] considered ETN "a transient adjustment reaction of the newborn skin to mechanical or thermal stimulation."

Still, others remain convinced that environmental stimuli play a role. A Chinese study of the epidemiology of ETN implicated various environmental factors.[15] Significantly increased rates of ETN were demonstrated among neonates with the following characteristics: term infant ($P<.05$), first pregnancy birth ($P<.001$), birth in the summer and autumn months ($P<.005$), fed with milk powder substitute or a mixed diet ($P<.001$), and vaginal delivery ($P<.001$). This study also suggested that the length of labor in neonates born by vaginal delivery is significantly correlated with the severity of ETN ($P<.001$).[15]

Because cultures fail to yield any pathogens, there has been little speculation that ETN may be triggered by microorganisms. However, with the utilization of modern technology, the possible role of microorganisms in the development of ETN is becoming more apparent. Immunohistochemical analysis has identified a number of inflammatory mediators involved in the pathogenesis of ETN, including IL-1α; IL-1β; IL-8; eotaxin; aquaporins 1 and 3; psoriasin; and nitric oxide synthases 1, 2, and 3.[21,22] The presence of these mediators suggests activation of the cutaneous immune system in response to microorganisms.[22]

In a 2005 study, Marchini et al[23] examined neonates with ETN using microbial cultures as well as scanning and transmission electron microscopy. They found microorganisms (likely staphylococci) localized to the follicular epithelium and internalized into surrounding immune cells. Therefore, it was suggested that ETN is a cutaneous immune reaction to "an acute, transitory attack of the commensal microflora" that penetrate the newborn skin via hair follicles.[23]

Clinical Manifestations

Erythema toxicum neonatorum is self-limited, usually beginning within 2 days of birth and resolving entirely within 6 days.[6,7,11] Occasionally, it appears at birth or 2 days later.[11,17,20,24-27] Recurrence occurs in up to 11% of neonates, between 5 and 11 days after the original eruption.[11] This transient neonatal rash is asymptomatic and resolves without sequelae.

Erythema toxicum neonatorum has been described as consisting of 2 variations: erythematopapular and pustular.[18] It occurs throughout the body, typically involving the face, trunk, and thighs; the palms, soles, and genitals are spared.[18,23] This pattern of involvement may be related to the distribution of hair follicles.[23]

The condition usually begins as erythema on the cheeks that rapidly spreads to the forehead and extremities. Erythema may be more difficult to detect on darker skin.[17] Within a few hours, macules tend to appear within and external to the erythema, beginning on the cheeks. A blotchy appearance ensues as the macules become confluent. These macules blanch on pressure and may resemble urticaria on the trunk.[11]

Erythematous macules often are evanescent, but where they persist, small central papules tend to appear. The papules are of a firm consistency and coloration evolves from pink to white or yellow within 24 hours. The papules also may arise de novo. Some papules may become superficial pustules, particularly on the skin of the back, buttocks, and abdomen. Although unusual, pustules may become secondarily infected. Pustules are 2 to 4 mm in diameter and contain pale yellow material. They are composed of more than 50% eosinophils. Peripheral blood eosinophilia of at least 7% and up to 15% frequently coexists.[18]

Erythema toxicum neonatorum was described in a neonate weighing 3150 g, presenting 2 days after birth and recurring for the final time as a papulopustule on the forehead on the 14th day (Figure). The neonate was a healthy term infant born to a 36-year-old primiparous woman by rapid and uncomplicated labor at 39 weeks' gestation and had an Apgar score of 9 at 5 minutes.

Diagnosis

The diagnosis of ETN usually is clinically evident. A cytologic specimen of pustule contents shows numerous eosinophils, with or without a small number of

A solitary vesicle of erythema toxicum neonatorum on the forehead of a 2-week-old neonate.

neutrophils.[11] The pustules do not contain less than 50% eosinophils and can approach 95%.[18] When the diagnosis is not clinically evident, a more thorough evaluation must be done to rule out an infectious etiology, which may include a workup to exclude sepsis; cultures of the pustules for bacteria, viruses, and fungi; serologic testing for neonatal varicella; and histologic evaluation including Wright and Gram stains.

Histopathology

Microscopic evaluation of erythematous macules and patches shows superficial dermal edema with a mild diffuse and perivascular eosinophilic infiltrate.[28] A few neutrophils, macrophages, and lymphocytes also may be evident. Papules display mild hyperkeratosis and a more pronounced edema with eosinophilic infiltration. The superficial layer of the pilosebaceous unit is most intensely involved, whereas the isthmus and inferior segment are, in general, completely spared. Hair follicles, eccrine glands, and ducts tend to be strongly affected. Pustules are subcorneal or intraepidermal and are associated with the pilosebaceous orifice in most cases. These pustules contain more than 50% eosinophils and a few neutrophils.[29]

Differential Diagnosis

The differential diagnosis includes sepsis, staphylococcal folliculitis, miliaria rubra, miliaria crystallina, pustular miliaria, congenital candidiasis, acne neonatorum, transient neonatal pustular melanosis (TNPM), infantile acropustulosis, neonatal varicella, and occasionally incontinentia pigmenti (Table).[30-34]

Transient neonatal pustular melanosis and incontinentia pigmenti should be easy to distinguish from ETN. The former is present at birth and often involves the palms and soles, lacks an erythematous component, and shows only neutrophils and cytologic debris.[35] However, TNPM and ETN may occur together. In addition, cases of TNPM have been described with the histologic features of ETN.[35,36] It has been suggested that TNPM may represent a precocious form of ETN.[36] Incontinentia pigmenti has vesicles filled with eosinophils but is more common in boys, is rarely pustular, and appears in a linear and more persistent pattern than ETN.[31]

Infantile acropustulosis can be differentiated from ETN by the distribution. Erythema toxicum neonatorum typically spares the palms and soles, while infantile acropustulosis characteristically involves the acral surfaces. Staphylococcal folliculitis, congenital candidiasis, and neonatal varicella are infectious processes and histologic examination can be used for differentiation.[29]

Treatment

To ease parental concern, it is important to educate them of the transient nature of the rash. Antihistamines have been shown to alter the duration of ETN.[10] However, the use of antihistamines is unnecessary and is not recommended because the rash does not seem to bother the child. The most useful therapy remains reassurance of the caregivers that the eruption is benign and will resolve without sequelae.[29]

Differential Diagnosis of Erythema Toxicum Neonatorum

- Acne neonatorum
- Congenital candidiasis
- Infantile acropustulosis
- Incontinentia pigmenti
- Miliaria crystallina
- Miliaria rubra
- Neonatal varicella
- Pustular miliaria
- Sepsis
- Staphylococcal folliculitis
- Transient neonatal pustular melanosis

Acknowledgment—This work is dedicated to Maria Koliou, MD, PhD, Archbishop Makarios III Medical Center, Nicosia, Cyprus, in admiration for her academic efforts.

REFERENCES

1. Taylor WB, Bondurant CP Jr. Erythema neonatorum allergicum: a study of the incidence in two hundred newborn infants and a review of the literature. *Arch Dermatol*. 1957;76:591-594.
2. Lehndorff H. Bartholomaeus Metlinger: a fifteenth century pediatrician. *Arch Pediatr*. 1951;68:322-333.
3. Smellie W. *A Treatise on the Theory and Practice of Midwifery*. 2nd ed. London, England: Wilson and Durham; 1752.
4. Steiner J. *Compendium der Kinderkrankheiten für Studirende und Äerzte*. Leipzig, Germany: FCW Vogel; 1873.
5. Moro E. Über dyspeptische exanthème bei säuglingen. *Gesellsch Kinderh*. 1910;12:9.
6. Mayerhofer E, Lypolt-Krajnovic M. Das erythema neonatorum toxicum—Leiner ("erythema papulatum" der alten artze) als teilerscheinung einer allgemeinen allergie der neugeborenen. *Z Kinderheilk*. 1927;43:630-657.
7. Mayerhofer E, Lypolt-Krajnovic M. Erythema neonatorum toxicum (Leiner) und allgemaine allergie der neugeborenen. *Wiener Klin Wschr*. 1927;40:991-995.
8. Finlay HV, Bound JP. Urticaria neonatorum (erythema toxicum neonatorum). *Arch Dis Child*. 1953;28:404-408.
9. Leiner C. *Über Eigenartige Erythemtypen und Dermatitiden des Frühen Säuglingsalters*. Leipzig, Germany: F Deuticke; 1912.
10. Levy H, Bagner AB. The effect of an antihistaminic substance (pyribenzamine) on erythema neonatorum. *Arch Pediatr*. 1951;68:413-416.
11. Harris JR, Schick B. Erythema neonatorum. *Am J Dis Child*. 1956;92:27-33.
12. Nanda A, Kaur S, Bhakoo ON, et al. Survey of cutaneous lesions in Indian newborns. *Pediatr Dermatol*. 1989;6:39-42.
13. Boccardi D, Menni S, Ferraroni M, et al. Birthmarks and transient skin lesions in newborns and their relationship to maternal factors: a preliminary report from northern Italy. *Dermatology*. 2007;215:53-58.
14. Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol*. 1986;3:140-144.
15. Liu C, Feng J, Qu R, et al. Epidemiologic study of the predisposing factors in erythema toxicum neonatorum. *Dermatology*. 2005;210:269-272.
16. González Echeverría F, Martínez Rodríguez J, Ancín Chandía T, et al. Is neonatal toxic erythema a risk factor in the development of allergy in childhood? [in Spanish]. *An Esp Pediatr*. 1997;47:515-520.
17. Carr JA, Hodgman JE, Freedman RI, et al. Relationship between toxic erythema and infant maturity. *Am J Dis Child*. 1966;112:129-134.
18. Duperrat B, Bret AJ. Erythema neonatorum allergicum. *Br J Dermatol*. 1962;73:300-302.
19. Keitel HG, Yadav V. Etiology of toxic erythema: erythema toxicum neonatorum. *Am J Dis Child*. 1963;106:306-309.
20. Levy HL, Cothran F. Erythema toxicum neonatorum present at birth. *Am J Dis Child*. 1962;103:617-619.
21. Marchini G, Ulfgren AK, Lore K, et al. Erythema toxicum neonatorum: an immunohistochemical analysis. *Pediatr Dermatol*. 2001;18:177-187.
22. Marchini G, Ståbi B, Kankes K, et al. AQP1 and AQP3, psoriasin, and nitric oxide synthases 1-3 are inflammatory mediators in erythema toxicum neonatorum. *Pediatr Dermatol*. 2003;20:377-384.
23. Marchini G, Nelson A, Edner J, et al. Erythema toxicum neonatorum is an innate immune response to commensal microbes penetrated into the skin of the newborn infant. *Pediatr Res*. 2005;58:613-616.
24. Marino L. Toxic erythema present at birth. *Arch Dermatol*. 1965;92:402-403.
25. Akoglu G, Ersoy Evans S, Akca T, et al. An unusual presentation of erythema toxicum neonatorum: delayed onset in a preterm infant. *Pediatr Dermatol*. 2006;23:301-302.
26. Chang MW, Jiang SB, Orlow SJ. Atypical erythema toxicum neonatorum of delayed onset in a term infant. *Pediatr Dermatol*. 1999;16:137-141.
27. Nanda S, Reddy BS, Ramji S, et al. Analytical study of pustular eruptions in neonates. *Pediatr Dermatol*. 2002;19:210-215.
28. Freeman RG, Spiller R, Knox JM. Histopathology of erythema toxicum neonatorum. *Arch Dermatol*. 1960;82:586-589.
29. Schwartz RA, Janniger CK. Erythema toxicum neonatorum. *Cutis*. 1996;58:153-155.
30. Shriner DL, Schwartz RA, Janniger CK. Impetigo. *Cutis*. 1995;56:30-32.
31. Janniger CK. Neonatal and infantile acne vulgaris. *Cutis*. 1993;52:16.
32. Feng E, Janniger CK. Miliaria. *Cutis*. 1995;55:213-216.
33. Urban J, Toruniowa B, Janniger CK, et al. Incontinentia pigmenti (Bloch-Sulzberger syndrome): multisystem disease observed in two generations. *Cutis*. 1996;58:329-336.
34. Ehrenreich M, Tarlow MM, Godlewska-Janusz E, et al. Incontinentia pigmenti (Bloch-Sulzberger syndrome): a systemic disorder. *Cutis*. 2007;79:355-362.
35. Ferrándiz C, Coroleu W, Ribera M, et al. Sterile transient neonatal pustulosis is a precocious form of erythema toxicum neonatorum. *Dermatology*. 1992;185:18-22.
36. Ramamurthy RS, Reveri M, Esterly NB, et al. Transient neonatal pustular melanosis. *J Pediatr*. 1976;88:831-835.