Neonatal Erythema Multiforme: A Case Report

Young Joon Cho, M.D.1, Sun Young Huh, M.D., Jong Soo Hong, M.D., Jae Yoon Jung, M.D., Dae Hun Suh, M.D.

Department of Dermatology, Seoul National University College of Medicine, 1Chois Skin Clinic, Seoul, Korea

Erythema multiforme (EM) is an extremely rare condition in infancy. To the best of our knowledge, there have been only three cases of neonatal EM described in the literature, and no such cases have been reported in Korea. A preterm neonate born at 35 weeks and six days of gestation presented with multiple annular erythematous patches with a targetoid shape over his entire body at 36 days of age (corrected age of 7 days). He had no systemic symptoms except for transient mild fever. No triggering factor except for hepatitis B and BCG vaccination was found. Neutropenia was noted upon laboratory analysis. Skin biopsy specimens showed findings suggestive of erythema multiforme. The skin lesions improved rapidly upon administration of intravenous methylprednisolone; however, neutropenia continued for a much longer period. The significance of neutropenia with respect to the development of EM was not clarified. There has been no recurrence of skin lesions over a one-year follow-up period. (Ann Dermatol 23(3) 382 ~ 385, 2011)

Keywords-
Erythema multiforme, Neonate, Neutropenia

INTRODUCTION

Erythema multiforme (EM) is an acute, self-limited disorder involving the skin and mucous membranes with common recurrences. EM is usually divided into two forms, EM minor and EM major. EM minor presents skin lesions without involvement of mucous membranes, while EM major is more severe, presenting both skin and mucous membrane lesions1,2. EM affects males more often than females, with a male:female ratio ranging from 3:2 to 2:1. Although it can occur in all ages, EM usually affects adolescents and young adults, and rarely occurs during infancy and childhood. Indeed, there have been only three cases of biopsy-proven EM during the neonatal period in the literature3-7. Here, we report a case of EM in a neonate.

CASE REPORT

A 36-day-old male preterm infant (corrected age of 7 days) was admitted to our hospital with complaints that skin lesions developed on his neck and inguinal area and then spread to his entire body within a day. The patient had been born at 35 weeks and 6 days of gestation, and had a birth weight of 3,150 g. The pregnancy was uncomplicated, and there was no remarkable family history or past medical history including infections or drug intake. The first dose of hepatitis B vaccination was administered after birth, and BCG vaccination, which is generally recommended in Korea, was administered at 30 days of age. Upon admission, the infant appeared well, with only low-grade pyrexia (37.5°C) that subsided the next day. His entire body was covered with well-defined annular erythematous patches of variable size, which were typical targetoid shape. The center of the round erythematous patches was darker than the periphery (Fig. 1). However, the face, palms, soles and mucous membranes were spared. The rest of his physical examination was normal. Laboratory evaluation showed neutropenia (total white blood cell [WBC] count 7.83 × 10^3/μl; normal 5.0 ~ 19.5 × 10^3/μl, absolute neutrophil count [ANC] 0.626 × 10^3/μl; normal 1.0 ~ 8.5 × 10^3/μl)8. Peripheral blood
Neonatal Erythema Multiforme: A Case Report

Fig. 1. (A) The entire body was covered by well-defined erythematous patches with a targetoid shape. (B) Typical targetoid lesions on left leg.

Fig. 2. (A) Histologic section showing a lymphocytic infiltration in the upper dermis with papillary edema (H&E, ×200). (B) Vacuolar change in the basal cell layer (black arrow), and necrotic keratinocytes (white arrow) within the epidermis (H&E, ×400).

smear was conducted and revealed some anisocytosis, poikilocytosis and lymphocytosis. However, these were not considered clinically significant. Serologic findings, including antibodies to herpes simplex virus and surface hepatitis B virus antigens, were negative. A skin biopsy specimen obtained from his right lower leg revealed a lymphohistiocytic infiltration in the upper dermis with papillary edema. Vacuolar degeneration of the basal cell layer and necrotic keratinocytes within the epidermis were also observed (Fig. 2). These findings were compatible with the diagnosis of erythema multiforme. The patient improved rapidly upon administration of intravenous methylprednisolone at a dose of 0.5 mg/kg/day for three days, followed by a tapering dose of oral methyl-
hepatitis B vaccination and candida infection. A case was described by Torrelo et al. in 2003 in a 3-week-old female. The girl had no involvement of the mucous membranes. Congenital hepatitis was diagnosed, but other microbiological and serological studies, including herpes simplex virus (HSV), showed no evidence of recent infection. The skin lesions spontaneously disappeared within two weeks without any treatment. The second case was reported by Johnston et al. in 2002 in a 25-day-old male. The patient had prodromal symptoms including rhinorrhea, fever, drowsiness and anorexia, which suggested an upper respiratory tract infection. He developed an unusual eruption with bullae and marked systemic symptoms. Chest X-ray revealed bilateral pulmonary infiltrates late in the course of the disease. There was no triggering factor. Symptoms began to resolve spontaneously after two weeks. The third case was described by Torrelo et al. in 2003 in a 2-week-old boy. The patient had no triggering factor for EM except for hepatitis B vaccination. However, hepatitis B antigens were not detected in the skin biopsy. The skin lesions cleared without scarring two weeks after the onset of the disease.

There were also several reports of neonatal EM without skin biopsy examination. Suggested etiologic factors of these cases included cow’s milk protein, drugs, hepatitis B vaccination and candida infection. In this case, the patient did not show any systemic symptoms except for transient mild fever. The short duration of fever and absence of lymphadenopathy, extremity changes and mucosal involvement excluded Kawasaki’s disease. In addition, we could not find any triggering factor for EM except for hepatitis B and BCG vaccination. Considering that EM is a reactive phenomenon that occurs 5~7 days after an initial insult, BCG vaccination, which was administered five days before the onset of the disease, could have been related to development of the skin lesions. Dermatological complications after BCG vaccination are rarely seen; however, they include specific skin reactions such as lupus vulgaris, scrofuloderma, regional lymphadenitis or tuberculid and nonspecific reactions such as keloid, urticaria, granuloma annulare or erythema nodosum. To date, there have been two reports suggesting an association of EM with BCG vaccination as a nonspecific reaction. These reactions may be mediated by immunological hypersensitivity reaction to antigens in the vaccine. However, the exact pathogenesis remains unclear.

Interestingly, neutropenia continued for a month. The ANC was 1.094×10^3/μl one month later and 5.03×10^3/μl 10 months later. At 1 year of follow up, there had been no recurrence or other systemic sequelae.

**DISCUSSION**

EM occurs commonly in adolescents and young adults. However, it has rarely been reported in neonates and infants. Moreover, to our knowledge, there have been only three cases of biopsy-proven EM during the neonatal period, and no such cases have been reported in Korea. The first case was demonstrated by Dikland et al. in 1986 in a 3-week-old female. The girl had no involvement of the mucous membranes. Congenital hepatitis was diagnosed, but other microbiological and serological studies, including herpes simplex virus (HSV), showed no evidence of recent infection. The skin lesions spontaneously disappeared within two weeks without any treatment. The second case was reported by Johnston et al. in 2002 in a 25-day-old male. The patient had prodromal symptoms including rhinorrhea, fever, drowsiness and anorexia, which suggested an upper respiratory tract infection. He developed an unusual eruption with bullae and marked systemic symptoms. Chest X-ray revealed bilateral pulmonary infiltrates late in the course of the disease. There was no triggering factor. Symptoms began to resolve spontaneously after two weeks. The third case was described by Torrelo et al. in 2003 in a 2-week-old boy. The patient had no triggering factor for EM except for hepatitis B vaccination. However, hepatitis B antigens were not detected in the skin biopsy. The skin lesions cleared without scarring two weeks after the onset of the disease.

There were also several reports of neonatal EM without skin biopsy examination. Suggested etiologic factors of these cases included cow’s milk protein, drugs, hepatitis B vaccination and candida infection. In this case, the patient did not show any systemic symptoms except for transient mild fever. The short duration of fever and absence of lymphadenopathy, extremity changes and mucosal involvement excluded Kawasaki’s disease. In addition, we could not find any triggering factor for EM except for hepatitis B and BCG vaccination. Considering that EM is a reactive phenomenon that occurs 5~7 days after an initial insult, BCG vaccination, which was administered five days before the onset of the disease, could have been related to development of the skin lesions. Dermatological complications after BCG vaccination are rarely seen; however, they include specific skin reactions such as lupus vulgaris, scrofuloderma, regional lymphadenitis or tuberculid and nonspecific reactions such as keloid, urticaria, granuloma annulare or erythema nodosum. To date, there have been two reports suggesting an association of EM with BCG vaccination as a nonspecific reaction. These reactions may be mediated by immunological hypersensitivity reaction to antigens in the vaccine. However, the exact pathogenesis remains unclear.

Interestingly, neutropenia continued for a month. The ANC was 1.094×10^3/μl one month later and 5.03×10^3/μl 10 months later. At 1 year of follow up, there had been no recurrence or other systemic sequelae.

**REFERENCES**

1. Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. J Am Acad Dermatol 1983;8:763-775.
2. Edmond BJ, Huff JC, Weston WL. Erythema multiforme. Pediatr Clin North Am 1983;30:631-640.
3. Weston WL, Morelli JG. Herpes simplex virus-associated
erythema multiforme in prepubertal children. Arch Pediatr Adolesc Med 1997;151:1014-1016.
4. Brice SL, Huff JC, Weston WL. Erythema multiforme. Curr Probl Dermatol 1990;2:3-26.
5. Dikland WJ, Oranje AP, Stolz E, van Joost T. Erythema multiforme in childhood and early infancy. Pediatr Dermatol 1986;3:135-139.
6. Johnston GA, Ghura HS, Carter E, Graham-Brown RA. Neonatal erythema multiforme major. Clin Exp Dermatol 2002;27:661-664.
7. Torrelo A, Moreno M, Prada I, Celma ML, Zambrano A. Erythema multiforme in a neonate. J Am Acad Dermatol 2003;48(5 Suppl):S78-79.
8. Custer JW, Rau RE, Lee CK. The harriet lane handbook. 18th ed. Philadelphia: Mosby, 2008:360.
9. Ashkenazi S, Metzker A, Rachnel A, Nitzan M. Erythema multiforme as a single manifestation of cow’s milk intolerance. Acta Paediatr 1992;81:729-730.
10. Nanda S, Pandhi D, Reddy BS. Erythema multiforme in a 9-day-old neonate. Pediatr Dermatol 2003;20:454-455.
11. Wine E, Ballin A, Dalal I. Infantile erythema multiforme following hepatitis B vaccine. Acta Paediatr 2006;95:890-891.
12. Korting HC, Vieluf D. Erythema multiforme and dermatitis seborrhoides infantum as concomitant id-reactions to widespread candidosis in a suckling. Mycoses 1991;34:415-417.
13. Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Nelson textbook of pediatrics. 18th ed. Philadelphia: WB Saunders, 2007:2744.
14. Dostrovsky A, Sagher F. Dermatological complications of BCG vaccination. Br J Dermatol 1963;75:181-192.
15. Dogliotti M. Erythema multiforme—an unusual reaction to BCG vaccination. S Afr Med J 1980;57:332-334.
16. Tschen EH, Jessen RT, Robertson G, Becker LE. Erythema multiforme as a complication of BCG scarification technique. Arch Dermatol 1979;115:614-615.
17. Baley JE, Stork EK, Warkentin PL, Shurin SB. Neonatal neutropenia. Clinical manifestations, cause, and outcome. Am J Dis Child 1988;142:1161-1166.
18. Funke A, Berner R, Traichel B, Schmeisser D, Leititis JU, Niemeyer CM. Frequency, natural course, and outcome of neonatal neutropenia. Pediatrics 2000;106:45-51.
19. James RM, Kinsey SE. The investigation and management of chronic neutropenia in children. Arch Dis Child 2006;91:852-858.
20. Weston WL. Steroids in erythema multiforme (EM). Pediatr Dermatol 2000;17:75-83.
21. Prendiville JS. Erythema multiforme and steroids. Pediatr Dermatol 2000;17:75-83.
22. Renfro L, Grant-Kels JM, Feder HM Jr, Daman LA. Controversy: are systemic steroids indicated in the treatment of erythema multiforme? Pediatr Dermatol 1989;6:43-50.
23. Rasmussen JE. Erythema multiforme in children. Response to treatment with systemic corticosteroids. Br J Dermatol 1976;95:181-186.