

Congenital CMV Infection with Blueberry-muffin Skin Lesions Showing Dermal Erythropoiesis

Seong Jin Kim, M.D., Mi Hye Lim, M.D., Seung Chul Lee, M.D., Young Ho Won, M.D.,
Inn Ki Chun, M.D., Young Ryun Choi, M.D.,* Chang Soo Park, M.D.**

Department of Dermatology, Pediatrics, Pathology**, Chonnam University Medical School,
Kwangju, Korea*

Blueberry muffin rashes occur in various diseases including TORCH syndrome, transfusion reactions, leukemia, hereditary spherocytosis and neonatal sepsis. We report a case of congenital CMV(cytomegalovirus) infection showing blueberry muffin skin lesions which revealed dermal erythropoiesis. Even though these cutaneous findings were nonspecific, they could provide a valuable clue in approach the congenital viral infection in the perinatal period.

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Congenital cytomegalovirus (CMV) infection is usually associated with neonatal purpura even though most cases are subclinical. Clinically, low birth weight, microcephaly, hepatosplenomegaly, jaundice and thrombocytopenic purpura are almost always present at birth and the diagnosis can be confirmed by serological examination with antibodies to CMV¹. Typical blueberry muffin rashes of CMV infection are known to represent dermal erythropoiesis rather than true petechiae and ecchymoses². However, dermal infiltration of nucleated erythrocytes can be seen in other viral diseases³ such as congenital rubella, toxoplasmosis, as well.

We report a case of generalized blueberry muffin lesions caused by congenital CMV infection showing dermal erythropoiesis.

REPORT OF A CASE

A newborn female was consulted in the NICU (neonatal intensive care unit) due to purpuric skin rashes since birth. The neonate was born at preterm (38 weeks + 1 day) by C-sec delivery as a re-

sult of careful observation of intrauterine growth retardation detected by antenatal ultrasonogram. The skin lesions were bluish red to violaceous annular macules and nodules (blueberry muffin rash) and were scattered on the face, trunk and extremities (Fig 1. A. B.). On examination cataracts and glaucoma, a heart murmur by atrial septal defect (ostium secundum type), and abdominal distension with huge hepatosplenomegaly were revealed. Measured body profiles included a low birth weight (2,130 gm) which was below the 10 percentile.

Routine laboratory examinations were as follows: WBC 5,800 /uL (lymphocytes 68%, neutrophil 28%) Hb 11.6 g/dL, PLT 180,000 /uL, nucleated RBC (+), platelets, APTT 36.1 sec, PT 12.1 sec, ALP 190 U, ALT 181 U, AST 425 U, Total bilirubin 15.7 mg/dL, BUN 9.2 mg/L, Sodium 140 mEq/L, Chloride 106 mEq/L, negative in VDRL and TPHA.

A Skin biopsy from the purpuric lesions showed scattered round cells with some extravasated RBCs (H-E, $\times 40$, Fig. 2) in the dermis. Infiltrated round cells were revealed as immature red cells under high power view (H-E, $\times 1000$, Fig. 3). With the impression of congenital viral infection, laboratory examinations were started to find out the causative virus and the results were as follows. TORCH screening with newborn and mother - 1) highly positive in newborn; CMV IgM, IgG,

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Reprint request to : Seong Jin Kim, M.D., Department of Dermatology, Chonnam University Medical School, Kwangju, Korea

Fig. 1. Generalized blueberry muffin rash showing bluish-red, infiltrated papules and purpura (A, B) .

clusion with lymphocytic infiltration in the portal area in addition to positive CMV in situ hybridization (Hybridization and detection assay systems, Pathogene, Enzo, U.S.A., Fig. 4). Rubella RNA screening by using PCR with 24S ss RNA12 (E1 subgenomic fragment, 1990~2230 nucleotide sequences, 321 bp) was negative.

Within three weeks, the purpuric skin lesions were lightened with conservative treatment by antithrombin III, vitamin K and D, antibiotics and phenobarbital.

DISCUSSION

CMV infection is known subclinically, it is therefore inapparent in most healthy adults who carry seropositive markers. However, in neonates and immunocompromised hosts, the morbidity and the mortality rates following symptomatic infection are now increasing. Neonates with CMV-seropositive mothers are exposed to the virus during the intrauterine period and perinatal care. Recently, the different modes of transmission on the basis of maternal age, socioeconomic status, and parity were suggested by the National Congenital Cytomegalovirus Disease Registry in United States⁴. Primary maternal CMV infection before the second trimester causes fetal neurological

Fig. 2. Histopathological findings under low-power view; scattered infiltration of round cells and red cells in the dermis (H-E, $\times 40$).

rubella IgG, herpes IgG, 2) positive in mother; CMV IgG, rubella IgG, herpes IgG. Histopathological findings of the liver obtained by needle biopsy revealed intracytoplasmic, intranuclear in-

Fig. 3. High-power view of specimen reveals nucleated RBC (normoblast) and immature cells (arrow heads, H-E, $\times 1,000$).

complications of microcephaly, intracranial calcifications, retinitis and optic nerve damages. These malformations share a similar clinical picture to the TORCH syndrome showing hepatosplenomegaly, jaundice, deafness, purpura (blueberry muffin baby)⁵. In symptomatic congenital CMV infection, intrauterine growth retardation and prematurity are significant findings as shown in our case.

Reported cutaneous manifestations of CMV infection are papules⁶, vesicles⁷, ulcerations^{7,8}, morbilliform rash⁹, petechiae and purpura¹⁰. In the case of congenital CMV infection, blueberry-muffin skin lesions composed of purpuric macules and papules are known to represent persistent dermal erythropoiesis. Dermal erythropoiesis is known to occur normally in the early developmental stage of the fetus. Therefore, persistence of these phenomena suggests that pathologic processes have been taking place such as tissue hypoxia and intrauterine viral infections which affect primitive mesenchymal tissues². However the differential diagnosis with rubella and toxoplasmosis from CMV infection is difficult unless there is more than a four fold increase in specific serological markers because both diseases also show dermal erythropoiesis. Furthermore, combined seropositivity in various viral markers of TORCH screening from mother and baby causes more confusion in accurate diagnosis. Fortunately, recent available primers in the PCR study made it possible to discriminate between those diseases¹¹. In our case PCR screening with rubella RNA¹² and CMV in situ hybridization were helpful for differential diagnosis in addition to screening for specific

Fig. 4. CMV in situ hybridization showed positively stained inclusion bodies.

antibodies.

Histopathological examination of the case showed scattered infiltrations of round cells in the dermis and a droplet of immersion oil enables us to recognize immature nucleated RBCs (normoblasts) easily under high power view (H-E stain, $\times 1000$). However, histopathological features in the skin including petechiae, purpura and dermal erythropoiesis are nondiagnostic as described above.

Other reported diseases causing blueberry muffin rash were twin transfusion syndromes¹³, coxsackie virus B-2 infection, Rh hemolytic disease of the newborn¹⁴, acute myelomonocytic leukemia¹⁵, congenital monoblastic leukemia¹⁶, hereditary spherocytosis, neonatal sepsis, etc.

Severely involved infants with congenital CMV were related to high mortality and late neurologic sequelae such as hearing loss, seizures, mental retardation and blindness. Although no effective therapy for congenital CMV has been available until now, newly developed antiviral agents such as acyclovir, ganciclovir and phosphonoformate (foscarnet) significantly reduced the mortality and the morbidity of CMV infection by using them with prophylactic measures or therapeutic regimens¹⁷. Nevertheless, early diagnosis and treatment is a cornerstone for a successful outcome in disseminated CMV infection.

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