In Utero Development of Neonatal Cutaneous Lupus

Sau-Pin Won, Chang-Sheng Yin[1]*, Hsiao-Hsuan Hsu, Kuei-Chen Huang[1], Hsiao-Ming Chiu[1]

Departments of Pediatrics, and [1]Obstetrics and Gynecology, Kong-Ning General Hospital, Taipei, Taiwan.

Neonatal lupus erythematosus (NLE) is characterized by cutaneous lupus, isolated congenital heart block (CHB), and a variety of systemic and hematologic abnormalities. The incidence of NLE is about 5–10% in mothers with systemic lupus erythematosus (SLE) [1]. Neonatal cutaneous lupus is a benign and self-limiting condition when it presents in isolation. The presence of anti-Ro autoantibodies in the affected infant's serum correlates with disease activity in the skin. The disease activity generally resolves by about the age of 6 months as the antibody titer decreases [2]. The mean time of detection of the skin rash ranges from birth to 20 weeks postpartum with a mean age at detection of 6 weeks. The rash is often exacerbated after exposure to UV light. In previous reports, only a minority (16–23%) of infants were found to have the rash at birth [2,3]. We report here a female baby who was born to an SLE mother with positive anti-Ro and anti-La; the baby already had an extensive skin rash at birth, suggesting that sun exposure was not a requirement for these skin lesions.

A woman aged 32 years, gravida 3, para 2, gave birth to a female baby with an extensive skin rash. The delivery was by cesarean section at 39^{+6} weeks of pregnancy because of breech presentation. The patient had been in good health until she was aged 31 years when, 3 months before this pregnancy, she developed a malar rash. An evaluation at a hospital led to the diagnosis of SLE. Low-dose prednisolone was administered but was discontinued by the patient herself after the pregnancy was diagnosed. Her obstetric history consisted of two normal spontaneous vaginal deliveries. Both female babies were normal. She had no other medical or surgical history, and did not take any medications after the pregnancy was detected. The whole course of the pregnancy was uneventful. There was no skin rash, arthralgia or myalgia during the pregnancy. An antenatal sonography at 20 weeks of pregnancy revealed no fetal cardiac arrhythmia. Her prenatal screening test for antibodies to rubella was positive and tests for syphilis and hepatitis B surface antigen were negative. Her laboratory tests at 39^{+6} weeks of pregnancy showed positivity for antinuclear antibodies (ANA) (1/2,560, speckled pattern), anti-Ro (1/575) and anti-La (1/721), but were negative for anti-ribonucleoprotein (RNP) and anti-Sm.

The female infant had a birth weight of 2,660 g, an Apgar score of 8 at 1 minute and 9 at 5 minutes. Meconium staining and an extensive skin rash were noted at birth. Widespread geographic erythematous annular and scaly plaques occurred over the face, scalp, trunk and legs, and were most marked on the face. The spectacle-like erythemas around her eyes gave a "mask" or "owl's eye"-like appearance (Figure 1). Some petechiae were displayed in her inguinal areas. A geographic erythematous plaque was seen over the left upper abdomen (Figure 2). There was no involvement of the conjunctiva or the vaginal mucosae. A 12-lead electrocardiogram showed a normal sinus rhythm and

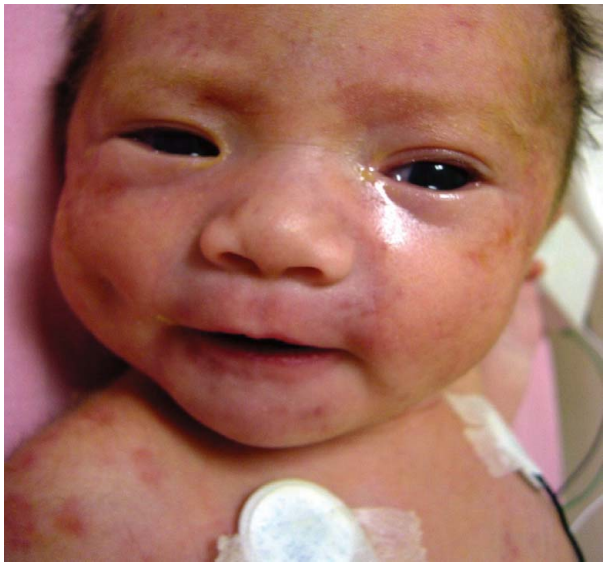

Figure 1. Spectacle-like erythemas around the eyes, giving a "mask" or "owl's eye" appearance.

*Correspondence to: Dr Chang-Sheng Yin, Kong-Ning General Hospital, No. 26, Lane 420, Section 5, Cheng-Kung Road, Taipei 114, Taiwan.
E-mail: khivf@mail.knh.org.tw
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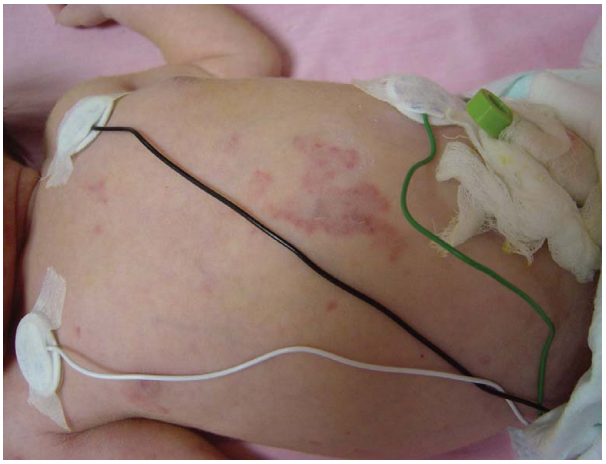

Figure 2. A geographic erythematous plaque over the abdomen.

echocardiography was also normal. Laboratory testing showed mild anemia (hemoglobin, 12.6 g/dL; hematocrit, 39.4%), moderate thrombocytopenia (34,000/mm^3) and mildly elevated liver enzymes (aspartate aminotransferase, 72 U/L). The blood coagulation studies were within normal limits. Serum tests gave a positive result for cytomegalovirus (CMV) IgG, but were negative for CMV IgM and herpes simplex virus type II IgG and IgM. An autoantibody profile showed positivity for ANA (1/1,280), anti-Ro (1/240) and anti-La (1/320), and negativity for anti-ds DNA, anti-cardiolipin and anti-phospholipid antibodies. A urine specimen was positive for group B streptococci antigen.

The infant was admitted to the intensive care unit because of progressive respiratory distress and moderate thrombocytopenia where she was treated with antibiotics and nasal continuous positive airway pressure ventilation support. Her condition became stable and no new skin lesions appeared; she was discharged 12 days after birth. Nearly all skin lesions had spontaneously faded by the age of 4 months.

SLE is a multisystemic disease involving the production of several autoantibodies, followed by immune complex formation and deposition with consequential clinical manifestations. Sunlight (UV light) exacerbates the disease, because UV light results in the crosslinking of DNA in cells. The release of DNA in an immunogenic form (UV crosslinked) can lead to autoimmunization. Pregnant woman with SLE have been shown to have an increased risk of fetal wastage, preterm birth, intrauterine growth restriction, and NLE [4].

Neonatal cutaneous lupus is a benign condition that develops in 5% of babies of mothers who may have SLE, Sjögren syndrome, or who may be entirely asymptomatic but with anti-Ro and anti-La autoantibodies. Neonatal cutaneous lupus frequently occurs during the second and third month of life, manifesting as a typical periorbital skin rash (mask or owl's eye appearance), when the baby is exposed to the UV present in sunlight and there is externalization of the intranuclear autoantigens at the cell surface. Female infants are more commonly affected, and this is attributed to increased anti-Ro expression by keratinocytes in response to estrogen [5].

In two previous large series studying neonatal cutaneous lupus, it was revealed that only a minority of cases, 16% and 23%, presented with a skin rash at birth [2,3]. In the report by Neiman et al [3], the mean age of appearance was 6 weeks and, in general, UV exposure is thought to be an initiating factor. Cimaz et al [6] reported a female infant born to an anti-Ro and anti-La negative, but anti-RNP positive mother, whose baby presented with an extensive NLE rash at birth. The authors suggested that sun exposure is not a requirement for the development of an NLE skin rash.

Differential diagnoses include intrauterine infection with CMV, intrauterine infection with group B streptococci, and noninfectious dermatoses of the neonate, such as erythema marginatum, urticaria, tinea corpus, erythema annulare centrifugum and erythema multiform. The most common clinical manifestations of congenital CMV infection are hepatosplenomegaly, intracranial calcifications, jaundice, growth restriction, microcephaly, chorioretinitis, and hearing loss. The skin lesions are vesicular, but they are rare and present only at birth. Thus in this case, congenital CMV infection was not likely. The reported skin lesions of the neonatal group B streptococci infection include vesicles, bulla, crusts and erosions, which were not seen in this case.

Erythema marginatum is the presence of pink rings on the trunk and inner surfaces of the arms and legs. The rings are barely raised, and the face is generally spared. Urticaria (wheals or hives) is characterized by elevated lesions caused by localized edema. Wheals are a common manifestation of hypersensitivity to drugs, stings/bites and autoimmunity. Tinea corpus is a fungal infection that manifests as multiple scaly patches varying in color from white to brown. Erythema annulare centrifugum appears as a raised pink-red ring or bull's eye marks, ranging in size from 0.5 cm to 8 cm. The erythema annulare centrifugum lesions are usually located on the buttocks, thighs and upper arms, and last for months or years. Erythema multiforme is characterized by target or iris skin lesions, and the oral mucosa may be involved. The classic lesion of erythema multiforme is annular, with a violaceous center and pink halo separated by a pale ring; the distribution is symmetric and centripetal. All the above cutaneous abnormalities were absent in our patient.

Meconium aspiration may have occurred with this full-term breech baby and may have been one of the causes of the respiratory distress syndrome after birth. Iatrogenic respiratory distress syndrome in newborns occurs even after cesarean section at 39 weeks of gestation with an absolute risk of 0.4% [7]. Neonates with congenital pneumonia also present with respiratory distress syndrome symptoms from very early in life.

There is a tendency for the subsequent pregnancies of women with autoantibodies to result in the birth of children with NLE. In the series of Neiman et al [3], the risk of CHB with or without rash in a subsequent birth was 30%. In 1999, Shinohara et al [8] administered betamethasone to mothers with SLE before 16 weeks' gestation and none of 26 neonates demonstrated CHB, whereas 15 of 61 neonates whose mothers received no corticosteroids or had begun receiving steroid therapy after 16 weeks' gestation showed CHB. The cause of CHB is presumed to be a widespread inflammatory response in the conduction system of the fetal heart caused by the transplacental maternal autoantibodies. The sinus node can be recognized in the first trimester, and the conduction system reaches functional maturity by week 16 of gestation. However, complete CHB once established is irreversible, and prenatal maintenance therapy with betamethasone given to the mother starting before 16 weeks' gestation would seem to reduce the risk of CHB in the offspring. Maternal corticosteroid therapy, however, does not seem to effectively prevent cutaneous lupus erythematosus [8]. The true incidence of NLE is not known, but Boh [9] estimated the rate as 1 in every 12,500 live births.

About half of the NLE babies have cutaneous lupus and the other half have CHB, with 10% having both [9]. CHB is a potentially fatal complication, and as a pacemaker is required in many cases, it is worthwhile counseling the SLE mother about the risk of CHB. All babies with NLE should be examined for CHB and later checked for the development of a rheumatic disease.

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