Langerhans Cell Histiocytosis in a Newborn

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A full-term female baby was admitted to our hospital at the postnatal age of 37 days with generalized vesiculopapular, crateriform skin lesions. Physical examination revealed a well-nourished baby without fever, hepatosplenomegaly or lymphadenopathy. Laboratory examination was normal except for thrombocytosis (platelet count, $970 \times 10^3/\mu L$). All studies for herpes simplex virus, including culture, polymerase chain reaction and IgM, were negative except for an antigen test from the vesicles for herpes simplex virus type 1, which was positive. Chest X-ray showed increased reticulogranular infiltration over bilateral lung fields and some osteolytic lesions at the left parietal bone. Skin biopsy revealed infiltration of Langerhans cells and eosinophils, plus positive CD1a and S-100 stains. The diagnosis was reconfirmed by a second hospital and chemotherapy was given. In this case report, the differential diagnoses of neonatal vesiculopapular skin lesions, and the classification and outcome of neonatal Langerhans cell histiocytosis are presented. [*J Chin Med Assoc* 2009;72(11):611–614]

Key Words: Langerhans cell histiocytosis, newborn, vesiculopapular skin lesion

Introduction

In newborns, there are various etiologies for papule, papule-vesiculae, pustulae or bullae skin lesions. Among infectious causes, viral infection such as congenital herpes simplex virus (HSV) carries the highest mortality if acyclovir treatment is not adequate; group B *Streptococcus* constitutes the most common perinatal bacterial infection. However, some noninfectious transient conditions, such as erythema toxicum neonatorum, require no medication. It is mandatory to obtain an accurate diagnosis for persistent skin lesions in newborns in order to prevent life-threatening consequences. Here, we report the case of a 1-month-old baby girl with vesiculopapular skin lesions who was otherwise well, who had poor response to acyclovir initially. Skin biopsy finally proved neonatal Langerhans cell histiocytosis (LCH).

Case Report

The baby girl was born by Cesarean section at 38 weeks of gestation to a healthy mother, with a birth body weight of 3,039 g. At the age of 10 days, she began to show generalized skin lesions, which were initially papules, followed by central vesicles, which finally became crateriform after crust formation. The mother did not pay much attention to them because the baby was otherwise well. At the age of 1 month, she was brought to a well-baby clinic for a routine check and vaccination. Admission was suggested under the impression of congenital herpes simplex infection. Tracing her family history, neither of her parents had any sexually-transmitted diseases or skin lesions suggesting herpes simplex infection.

On admission, the girl was alert and thriving, with a body weight of 4,430 g. The vital signs were normal, breathing sounds were clear, heart rate was regular, and a neurological examination was normal. There was no fever, hepatomegaly or lymphadenopathy. The skin lesions, scattered over the scalp, face, oral mucosa, 4 extremities, trunk and buttocks, were crateriform papulovesicular with crust in the center (Figure 1). Blood test showed hemoglobin level of 11.7 g/dL, white blood cell count of 12,600/μL, neutrophilic segments, lymphocytes and monocytes of 35%, 57% and 8% respectively, platelet count of $970 \times 10^3/\mu L$,

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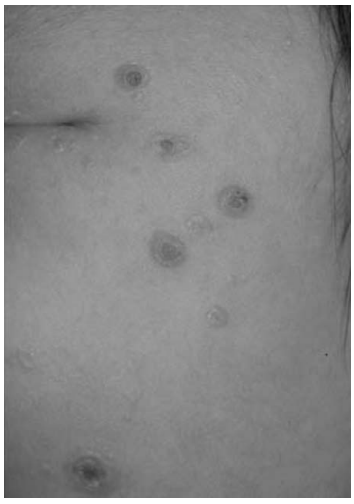

Figure 1. Crateriform papule-like vesicles with center crust on the face of the infant.

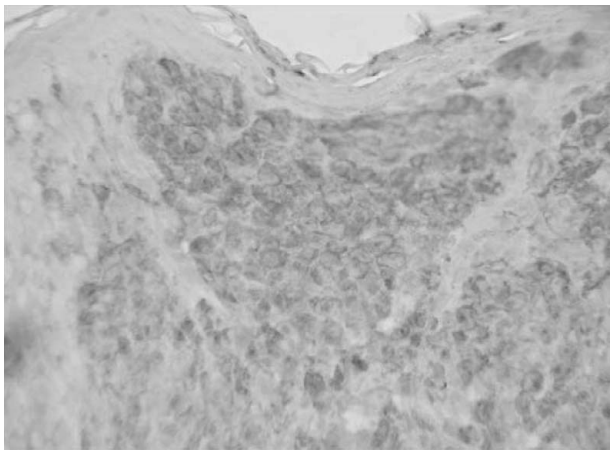

Figure 2. Skin biopsy positive for CD1a: predominant stain in membrane and weak cytoplasmic reactivity.

and C-reactive protein < 0.1 mg/dL. Lumbar puncture and brain sonography revealed no abnormalities. Viral antigens and cultures were all negative except for the antigen of type 1 HSV, which was positive.

Initially, she received intravenous acyclovir (10 mg/kg/dose, q8h). However, the eruption of papulovesicular lesions continued, so acyclovir was discontinued and a skin biopsy was performed. Microscopically, the epidermis showed focal spongiosis with eosinophil exocytosis. In addition, loosely aggregated large cells, some of which showed infolded/vesicular nuclei, were seen in the epidermis and papillary dermis. A small amount of mitosis was also noted. These large cells were weakly positive for S-100 protein and strongly positive for CD1a (Figure 2). In the upper dermis, there was mild perivascular infiltration of inflammatory cells composed of eosinophils and lymphohistiocytosis.

Tzanck smear showed no inclusion bodies. Diagnosis of LCH was confirmed, and a systematic survey was done. Routine skull radiography revealed an osteolytic lesion in the left parietal area (Figure 3), and chest X-ray showed mild reticulonodular infiltration. Abdominal sonography and biochemical tests including erythrocyte sedimentation rate, prothrombin time/activated partial thromboplastin time, fibrinogen, transferrin, total protein, alkaline phosphatase and lactate dehydrogenase were normal.

Chemotherapy was suggested, but the family took the baby to a second hospital where a diagnosis of LCH was reconfirmed. She was initially treated with a low-risk group regimen according to the guidelines of the Taiwan Pediatric Oncology Group 2003 for LCH, with prednisolone and vincristine for the first course. The regimen was shifted to vincristine and methotrexate (MTX) plus prednisolone (high risk group) due to

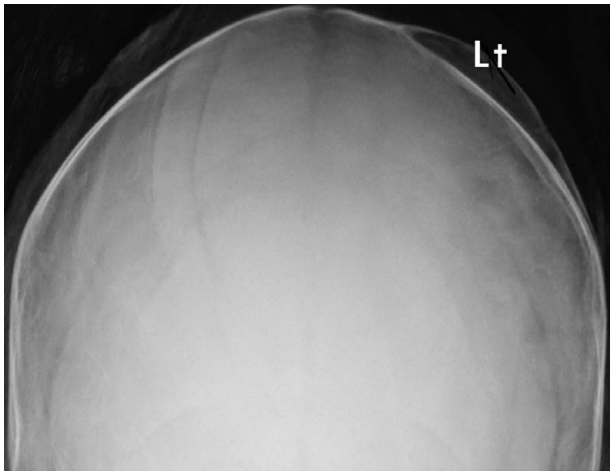

Figure 3. Osteolytic lesions on the left parietal bone of the skull.

lung involvement. The skin lesions regressed after the second course of chemotherapy.

The patient is now 16 months old, with a body weight of 8.6 kg and body length of 76 cm. The whole course of chemotherapy was completed, with no active lesions remaining.

Discussion

Neonatal skin lesions are a common problem for both parents and physicians. The etiology ranges from a transient benign nature to serious underlying disease. A health care provider should be aware of abnormal lesions and provide adequate and timely intervention to prevent devastating consequences. In this female infant with vesiculopapular lesions, both infectious and noninfectious causes were considered. Infectious

causes include HSV, varicella, cytomegalovirus, group A or group B *Streptococcus*, *Staphylococcus aureus*, *Listeria*, *Pseudomonas* and *Candida albicans*. Non-infectious causes include erythema toxicum neonatorum, transient pustular melanosis, eosinophilic pustular folliculitis and, rarely, LCH, epidermolysis bullosa as well as congenital leukemia. Due to the high mortality rate of most of the infectious causes of neonatal skin lesions, we provided both antibiotics and acyclovir before the infectious causes were eliminated. In newborns, HSV infection carries a high mortality rate: without antiviral therapy, the mortality rate is 80%[1] and with therapy, it is nearly 30%.[2] In bacterial infections, group B *Streptococcus* and *S. aureus* are the most common pathogens; the former may lead to bacteremia, meningitis and pneumonia and the latter, called impetigo neonatorum, may cause osteomyelitis, pneumonia, sepsis and staphylococcal scalded skin syndrome. Therefore, in newborns, it is necessary to start early therapy even in the absence of a definite confirmation of the causative organism. In this well-appearing infant, bacterial sepsis was unlikely, and HSV could be ruled out because the virus cultures, PCR as well as Tzanck smear, were negative, and the response to acyclovir treatment was poor. Finally, skin biopsy revealed dermal infiltration of histiocytes that were positive for CD1a and S-100 stain. Thus, a diagnosis of LCH was made.

The histiocyte group, the monocyte-macrophage system of bone marrow origin, contains monocytes, macrophages and dendritic cells, which serve as antigen-presenting cells. LCH is a clonal proliferative disorder of Langerhans cells. It constitutes a dysregulated immune response with unsuccessful transition from "innate" to "adaptive", which leads to a lack of plasma cells at the lesion site.[3] The first presentation of LCH was made by Paul Langerhans under an electron microscope. The characteristic picture is Birbeck granules, which are present in the cytoplasm and look like tennis rackets.[4]

In the past, LCH had the eponymous nomenclature of histiocytosis X due to its unclear pathogenesis. The histiocytic disorders are divided into 3 different groups: (1) dendritic cell histiocytosis (to which LCH belongs); (2) erythrophagocytic macrophage disorders; and (3) malignant histiocytosis. Although the disease mechanism is an abnormal proliferation of cells, in the absence of aneuploidy, metaphase or karyotypes, it is hard to define LCH as a neoplastic disorder. Also, the prognosis is diverse, ranging from excellent survival without organ involvement to multiple organ infiltration requiring chemotherapy; self-limiting disease has also been reported.

LCH can occur at any age; children below 15 years of age have a higher incidence rate of 8.9 persons per million,[5] and neonates below 28 days of age 1–2 persons per million.[6] In Taiwan, the incidence during 1995–1999 was 1.37–3.29 per million children per year.[7] The clinical presentation is single-organ or multiorgan invasion of the skin, bone, lymphatic system, liver, spleen, lungs and central nervous system. Skin manifestations are often the first lesions to be recognized.[8] During the neonatal stage, such as in our case, it usually presents as erythematous pustular vesicles with crateriform ulceration and scaling, which often leads to the misdiagnosis of congenital infectious disease. At older ages, lesions are scaly and seborrhea-like in the groin or scalp area.[9]

Hashimoto et al[10] described a congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease) with cutaneous lesions, mostly in the neonate stage. However, many studies have discovered that, though referred to as self-healing, some cases have multiorgan invasion in the initial diagnosis while others have relapse or multiorgan involvement later in life.[11] A retrospective study conducted by Stein et al[11] found that among 19 infants who had cutaneous eruptions before the postnatal age of 4 weeks and who were diagnosed with LCH later, 7 patients had skin lesions only, while the other 12 patients had multiorgan involvement, of whom 2 died. Greenberger et al[12] found that children younger than 2 years of age and with multiorgan involvement had a higher mortality rate. Thus, comprehensive evaluation of all children with cutaneous LCH is mandatory.

Treatment is not based on the subtype of LCH. Instead, it depends on the organs involved. According to the guidelines of the Taiwan Pediatric Oncology Group 2003, LCH is divided into high-risk and low-risk groups, for which the treatments are different. The low-risk group is defined as patients older than 2 years without liver, bone marrow or lung involvement. Patients with multiorgan involvement and dysfunction of the liver, lungs or bone marrow are enrolled in the high-risk group. The localized cutaneous lesions can be treated with steroids or short-term nitrogen mustard or psoralen plus ultraviolet A therapy. Surgical resection can be performed for localized cutaneous nodules or single solitary bone lesions.

Chemotherapy for the low-risk group starts with prednisolone (40 mg/m^2/day) and vincristine (1.5 mg/m^2/dose, intravenous, weekly for 4 doses) for 6 weeks followed by continuation therapy of prednisolone (40 mg/m^2/day 5 days tri-weekly), vincristine (1.5 mg/m^2/dose tri-weekly) and 6-mercaptopurine (50 mg/m^2/day) for a total of 52 weeks of treatment.

In the high-risk group, the initial therapy is composed of MTX (500 mg/m^2 biweekly for 2 doses), prednisolone (40 mg/m^2/day) and vincristine (1.5 mg/m^2/dose weekly for 4 doses) lasting for 6 weeks, followed by MTX (20 mg/m^2 weekly) with the same regimen of continuation therapy as in the low-risk group for 52 weeks of therapy. In this protocol, MTX is regarded as the effective drug to maintain disease-free status. Prognosis depends on the organs involved, dysfunction of the organs and the response to the chemotherapy.[13]

In Taiwan, Chen et al[7] pointed out that local treatment and disseminated LCH contributes to a high risk of LCH aggressiveness. Patients who died initially presented with multisystem involvement and organ dysfunction including fever, anemia and thrombocytopenia, which progressed to pancytopenia, refractory skin involvement, massive hepatosplenomegaly and multiorgan failure leading to death.

In conclusion, the skin manifestation of neonatal LCH is always papulovesicular eruptions that mimic other infectious diseases. It is not over-treatment to give antibiotics or antiviral agents initially before the condition has been proved to be a noninfectious disease. For unusual or persistent skin lesions, skin biopsy with histopathologic and immunohistochemical studies are required to confirm the etiology. This case report demonstrates the importance of skin biopsies, which can shorten the course to reach an accurate diagnosis and provide timely intervention in such cases. It is prudent to bear in mind the diagnosis of congenital self-limiting LCH (Hashimoto-Pritzker disease) in newborns. An intensive systematic survey of the organs involved is required. Even if the child only has cutaneous lesions, long-term surveillance is indicated because it is possible to relapse or for multiorgan involvement to occur later.

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