Case Report

Cutaneous Manifestation of Langerhans Cell Histiocytosis in Neonate: A 3 Cases Report and Literature Review

Rujimethapass N, MD[1], Chanveerachai S, MD[1], Limpongsanurak W, MD[1], Singalavanija S, MD[1]

[1] Dermatology Unit, Queen Sirikit National Institute of Child Health, Bangkok, Thailand

Background: Langerhans cell histiocytosis (LCH) is a group of disorders that encompasses a wide range of disease spectrum from localized spontaneous remission to systemic involvement. It is uncommon in neonatal period. Cutaneous manifestation is the most common presentation in neonatal onset LCH. Skin lesions vary from single solitary nodule to generalized cutaneous eruption.

Case Report: The present authors reported three cases that include two males and one female. All cases were presented with generalized, discrete erosive papules with hemorrhagic crusts since birth. In all cases, physical examinations were normal. Laboratory investigations including complete blood cell count, chemistry panel, urinalysis, and liver function tests were unremarkable. Bone survey shown no osteolytic lesion. Skin biopsy with immunohistologic staining was performed and confirmed diagnosis of LCH in all cases. Skin lesions improved in few weeks later with no other systemic symptoms in all cases. At the six-week follow-up, one case developed high fever and hepatosplenomegaly. A few months later, it was diagnosed as LCH with systemic involvement by a pediatric oncologist.

Conclusion: Cutaneous manifestation is the common presentation of LCH in neonate. Although the majority of patients are benign, skin-only and self-limiting clinical course, careful physical examination and long-term follow-up for systemic involvement are mandatory.

Keywords: Langerhans cell histiocytosis, Cutaneous manifestation, Neonate

J Med Assoc Thai 2019;102(11):1248-53
Website: http://www.jmatonline.com
Received 18 Jul 2019 | Revised 27 Sep 2019 | Accepted 30 Sep 2019

Langerhans cell histiocytosis (LCH) is a group of disorders characterized by the proliferation of activating histiocytes infiltrated and accumulated in various tissues. Activated histiocytes contain birbeck granules in their cytoplasm, with positive immunostaining for protein S100 and CD1a[1]. It occurs in 1 in 200,000 children less than 15 years of age and less often in adults[2,3]. The pathogenesis of LCH is controversial. Recent study has revealed mutations in the Ras/Raf/MEK (mitogen-activated protein kinase kinase)/ERK (extracellular signal-regulated kinase) (Ras-ERK) pathway providing more definitive support for classification of LCH as a neoplasm[4]. Numerous tissues might be affected to a variable extent, including skin, bone, lymph node, pituitary, lung, liver, spleen, and hematopoietic cells. Nevertheless, bone and skin involvement are most common[5]. Cutaneous involvement is the most common presenting symptoms of LCH in young children of less than two years, which varies from self-limiting localized (Congenital self-healing Langerhans cell histiocytosis, CSH-LCH) to disseminated organ dysfunction and grave prognosis[6,7].

The term CSH-LCH so called Hashimoto-Pritzker disease described neonatal onset of skin lesion commonly as a widespread eruption of cutaneous red-brown nodules that resolves spontaneously without involvement of other organs[8-12]. Currently, there are no criteria other than clinical that can reliably distinguish the localized cutaneous form of LCH from the disseminated type. Many studies have investigated the diagnostic role of immunohistochemical stains and histologic criteria to differentiate CSH-LCH from disseminated form, which is controversial[6,8,9,13-15]. While CSH-LCH generally follows a benign clinical

Correspondence to:

Singalavanija S.

Dermatology Unit, Queen Sirikit National Institute of Child Health, 420/8, Rajvithi Road, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-3548439 ext. 4333, **Fax**: +66-2-3548439

Email: singal2498@gmail.com

How to cite this article: Rujimethapass N, Chanveerachai S, Limpongsanurak W, Singalavanija S. Cutaneous Manifestation of Langerhans Cell Histiocytosis in Neonate: A 3 Cases Report and Literature Review. J Med Assoc Thai 2019;102:1248-53.

course; nonetheless, evaluation for systemic disease and long-term follow-up is essential. According to the Histiocyte Society, the evaluation of patients with any form of LCH should include physical examination, full blood count, coagulation studies, liver function tests, urine osmolality, complete skeletal radiographic survey, and chest X-rays to be repeated every six months[16].

Cutaneous manifestations of LCH in the neonatal period are commonly described as vesiculopustules with petechial and hemorrhagic crust or single nodular, ulcerative lesion. The authors reported cases of LCH presented with quite similar cutaneous presentations since birth but different clinical outcome in Queen Sirikit National Institute of Child Health over a 5-year period.

Case Report

Medical records of three patients presented with skin lesion, biopsy proven LCH, since birth at Queen Sirikit National Institute of Child Health between March 2010 and October 2015 were reviewed. The maternal age, gestational age, age at diagnosis, gender, presenting symptoms, characteristics, and distribution of skin lesions, organ involvement, timing of improvement, treatments, and disease progressions were recorded. Diagnoses of all patients were made by skin biopsy sent for histoimmunochemistry (S100, CD1a). Skin characteristics were noted and recorded by photography at the time of diagnosis.

Case 1

Term newborn, male presents with skin eruption noted at birth. Labor was uneventful, his birth weight was 2,778 grams. Tachypnea developed within few hours after birth and was diagnosed as transient tachypnea of the newborn. The mother, 21 years old G1P1, was reported complete medical care during the prenatal period. She denied febrile illness, skin eruption, or sexually transmitted diseases during the prenatal period. She took no medications and denied illicit drug use. Maternal serologies were negative for hepatitis C or hepatitis B surface antigen. On the physical examination, there were generalized purpuric and erythematous papules with hemorrhagic crust involving palm and sole (Figure 1, 2) neither hepatosplenomegaly nor lymphadenopathy was present. Laboratory studies obtained at birth, including complete blood cell count, chemistry panel, urinalysis, and liver function tests, were normal. Culture and potassium hydroxide (KOH) preparation from the lesions were all negative. Skin biopsy was performed and showed epidermal ulceration and infiltrated by histiocytes with mixed eosinophils infiltrated in the

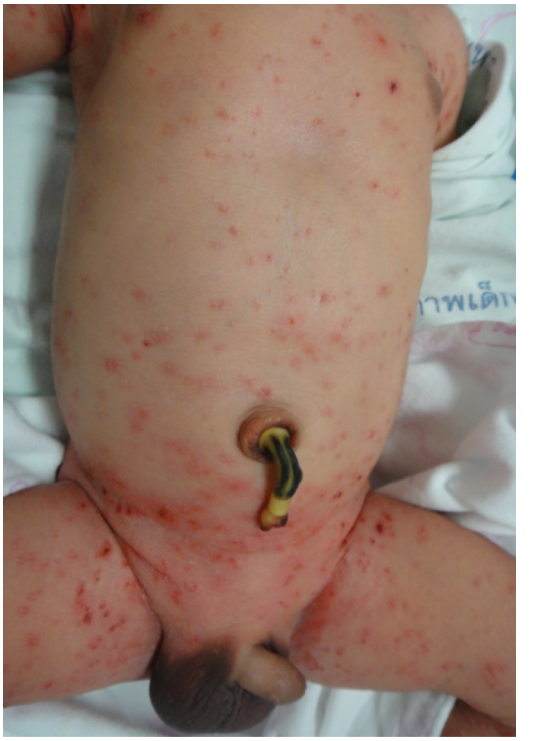

Figure 1. Seborrheic-like lesion with scaling and petechiae (with permission from parents).

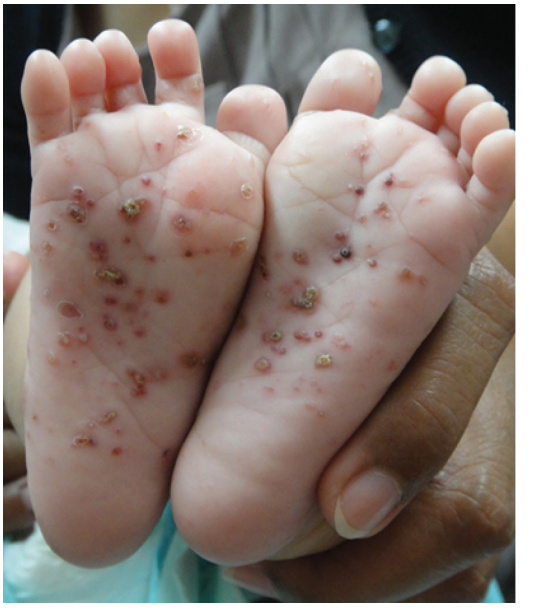

Figure 2. Crusted erythematous vesiculopustules on both soles (with permission from parents).

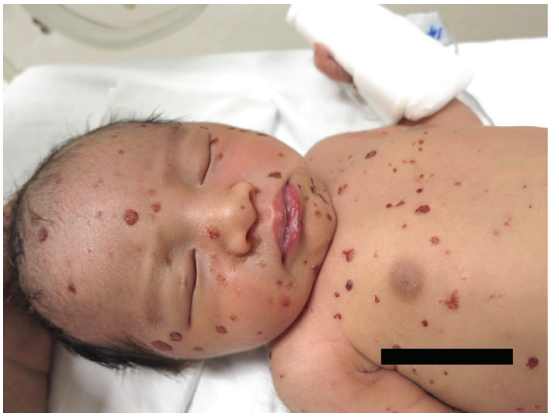

Figure 3. Generalized erosive papules which evolved to hemorrhagic crusted (with permission from parents).

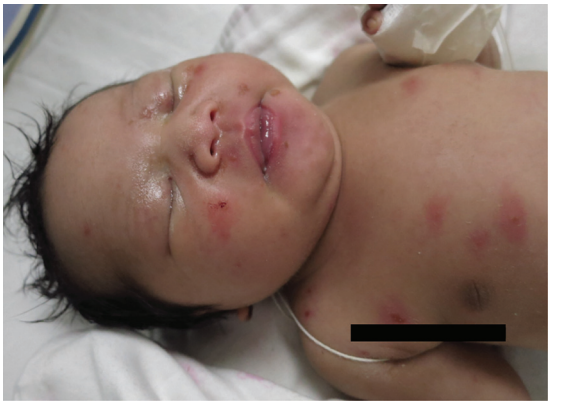

Figure 4. Generalized erythematous papules with hemorrhagic crusted (with permission from parents).

dermis. Immunohistochemical staining for CD1a and S100 were positive. Film skull bone survey shown no osteolytic lesion. The diagnosis of LCH without systemic involvement was made. The patient was stable after seven days of cloxacillin and gentamycin and was discharged home. Patient presented at the hospital one month later due to acute fever, abdominal distension, and progressive weight loss. On the physical exam, he was anemic with widespread petechiae at face, scalp, abdomen, and back, as well as hepatosplenomegaly. Bone marrow aspiration showed increase in hemophagocytic activity. The diagnosis of LCH with systemic involvement was made and he was treated and follows up with hemato-oncologist.

Case 2

Male, full term newborn presented with diffuse cutaneous nodules since birth. He was born at 37 weeks to a 25-year-old gravida 4 para 3 mother by vaginal delivery. Routine antenatal cares were unremarkable. Upon delivery, the baby was in mild respiratory distress due to hypoglycemia, which improved after blood sugar level returned to normal. Physical examination revealed diffuse erosive and hemorrhagic papules and few infiltrative nodules on the face, trunk, extremities, and both soles (Figure 3). Laboratory studies obtained at birth, including complete blood cell count, chemistry panel, urinalysis, and liver function tests, were normal. TORCH titer, hemoculture were negative. Gram's stains showed few polymorphonuclear neutrophils (PMN) with no organism and negative Tzanck smear for multinucleated giant cells. A punch biopsy specimen of infiltrative subcutaneous nodule from the abdomen was obtained. Hematoxylin and eosin stain of the skin biopsy specimen revealed scale-crust epidermis, dense lichenoid mixed cellular infiltrate composing of histiocytes few eosinophils and medium to large-size mononuclear cells with irregular-shaped nuclei. Immunohistochemical staining was strongly positive with anti-S100 and CD1a. A diagnosis of LCH was made, and a pediatric oncologist was consulted. Pediatric bone surveys, a chest X-ray showed no evidence of systemic involvement. The patient was given intravenous cloxacillin and gentamycin for seven days and was stable for discharge on day-of-life 10. The cutaneous lesions completely resolved over the next two months, leaving hypopigmented macules. Patient remained healthy during four years of follow-up.

Case 3

Female newborn had a generalized skin eruption since birth. The female infant was born via spontaneous vaginal delivery at 40 weeks gestation without complications. Her birth weight was 2,846 g. The mother, 32 years old G1P1, was reported complete medical care during the prenatal period. On the physical examination, she was a healthy-appearing, non-dysmorphic full-term newborn with multiple discrete erosions and hemorrhagic crusts on the face, trunk, extremities, and both soles (Figure 4). There were no hepatosplenomegaly and otherwise unremarkable. Complete blood cell count, chemistry panel, urinalysis, and liver function tests, were normal except for a slightly elevated white blood cells count of 19,680 /mm^3. Pediatric bone surveys and a chest X-rays were unremarkable. Punch skin biopsy showed dense mononuclear cells infiltration composed of lymphocytes and large mononuclear cells that had hyperchromatic and bean-shape nuclei.

Table 1. Demographic data, clinical presentation, treatment and outcome of all patients

	Case 1	Case 2	Case 3
Maternal age	21 years	25 years	32 years
Gestational age	38 weeks	38 weeks	40 weeks
Sex	Male	Male	Female
Age at presentation	At birth	At birth	At birth
Age at diagnosis	2 days	2 days	2 days
Presenting symptoms	Skin lesions	Skin lesions	Skin lesions
Number of skin lesions	Multiple	Multiple	Multiple
Location of lesions	Face, trunk, extremities, palms and soles	Face, trunk, extremities, palms and soles	Face, trunk, extremities, palms and soles
Characteristic of skin lesions	Ulcerated papules, petechiae, crusts	Erosions and hemorrhagic crusts	Erosions and hemorrhagic crusts
Timing of systemic involvement	8 weeks	None	None
Organ involvement	Hematology Liver Spleen Lymph node Bone	None	None
Treatment	Vinblastine Prednisolone Methotrexate Etoposide	None	None
Duration of follow-up	7 years	4 years	2 years
Clinical course	Systemic involvement	Self-limiting	Self-limiting

Immunohistochemical staining was strongly positive with S100 and CD1a, confirming the diagnosis of LCH. Patient was treated with empirical intravenous antibiotics and routine skin care. On two weeks follow-up all lesions were healed without scarring. Duration of follow-up period was two years.

Results

There were three patients who presented skin lesions at birth. Two patients were male and one was female. All cases were presented with skin eruptions since birth. Cutaneous findings described as generalized, discrete erosive papules with hemorrhagic crusts in all cases. Physical examination other than skin and laboratory investigation including complete blood cell count, chemistry panel, urinalysis, liver function tests were unremarkable and skull, bone survey shown no osteolytic lesions. Skin biopsy with immunohistologic staining was performed and confirmed diagnosis of LCH in all cases. Skin lesions disappeared one to two months later with no other systemic symptoms in two cases. One case developed high fever and hepatosplenomegaly two months later and was diagnosed as LCH with systemic involvement by a pediatric oncologist (Table 1).

Discussion

The LCH is a disorder of activating histiocytes or Langerhans cells. It has a wide range of disease spectrum, which is comprised of localized spontaneous remission, so called Hashimoto-Pritzker disease, to multiples organ involvement especially the liver, spleen, and bone marrow[9]. To diagnose LCH, patients must have characteristic clinical feature in collaboration of histologic and immunohistologic results[17,18]. As cutaneous manifestation is the most common presentation of LCH in young children, a skin biopsy rapidly provides an accessible mean to diagnosis[5]. Typical skin lesions seen in neonatal periods commonly show vesiculopustular lesions or erosive brownish papules, vesicles, and mostly developed hemorrhagic crusts scattered all over the body. However, single solitary lesions or, blue-purplish to dark red popular eruptions, so-called blueberry

muffin baby has also been reported[5,19-22]. In general pediatrics practice, cutaneous manifestation of LCH should be distinguished from other vesiculopustular lesion occurring at birth, including infectious causes such as herpes simplex infection, neonatal varicella, congenital syphilis or congenital candidiasis or non-infectious process such as neonatal pustular melanosis, incontinentia pigmenti, eosinophilic pustular folliculitis or congenital leukemia cutis. Gram stain, culture, KOH, and Tzanck smear should be done to rule out an infection cause. The authors describe three cases of congenital onset of LCH presented with generalized typical erosive papules and pustules with hemorrhagic crusts at birth. One of them has progress to systemic LCH and the others resolved in a few months. From literatures review, many authors described the term CSH-LCH as neonatal onset asymptomatic solitary or multiple skin lesion that resolve spontaneously during the first two to three months with relatively good prognosis[8,10-12,21]. Unfortunately, like in the present studies, not all of the case resolve. In the present series, three patients presented with similar typical cutaneous eruptions at birth, and one progressed to systemic LCH, resulting in a progression rate of 33%, which is similar to 30% in the DAL/HX 83/90 studies[23]. Predictors of disease progression or recurrence, or survival remain to be known. Many studies have investigated the diagnostic role of immunohistochemical stains and histologic criteria to differentiate CSH-LCH from disseminated form, which is still controversial[6,13-15,24]. Simko et al studied the correlation between skin manifestations and multisystem involvement in LCH patients and found that skin eruption in patients older than 18 months of age at diagnosis was associated with the presence of multisystem disease[25]. However, the present study also found that cutaneous eruption of LCH that developed during the first week of life was not always correlated with a good prognosis. In Stein et al and Battistellaa et al, the study suggested that the extent of systemic involvement of LCH cannot be predicted based on clinical presentation, thus the term "Hashimoto Pritzker disease" or "self-healing LCH" can be made only by retrospectively mean and should not be used to describe patients with active disease[5,24].

Conclusion

While some of the cases are skin-only, self-limiting clinical course, a number of patients progressed to skin plus multisystem LCH[10,26,27]. Thus, patients diagnosed as LCH, even in only one organ system, must undergo a thorough physical examination and laboratory evaluation according to current recommendations of the Histiocyte Society[16]. The authors also suggest a long-term follow-up since some may reappear and progress after complete resolution.

What is already known on this topic?

Onset of LCH, a cutaneous manifestation common in neonatal, is mostly benign.

What this study adds?

Characteristic of skin lesion and onset of disease cannot predict clinical course. Prompt and regular screening and follow-up is essential for patients presenting with cutaneous presentation of Langerhans cell histiocytosis.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Riva B, Restano L, Gelmetti C. Two cases of a solitary congenital ulcerated nodule. Pediatr Dermatol 2009;26:473-4.
2. Grana N. Langerhans cell histiocytosis. Cancer Control 2014;21:328-34.
3. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. Pediatr Clin North Am 2015;62:139-65.
4. Tran G, Huynh TN, Paller AS. Langerhans cell histiocytosis: A neoplastic disorder driven by Ras-ERK pathway mutations. J Am Acad Dermatol 2018;78: 579-90.
5. Stein SL, Paller AS, Haut PR, Mancini AJ. Langerhans cell histiocytosis presenting in the neonatal period: a retrospective case series. Arch Pediatr Adolesc Med 2001;155:778-83.
6. Kapur P, Erickson C, Rakheja D, Carder KR, Hoang MP. Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease): ten-year experience at Dallas Children's Medical Center. J Am Acad Dermatol 2007;56:290-4.
7. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. N Engl J Med 2018;379:856-68.
8. Hashimoto K, Pritzker MS. Electron microscopic study of reticulohistiocytoma. An unusual case of congenital, self-healing reticulohistiocytosis. Arch Dermatol 1973;107:263-70.
9. Krooks J, Minkov M, Weatherall AG. Langerhans cell histiocytosis in children: History, classification, pathobiology, clinical manifestations, and prognosis. J Am Acad Dermatol 2018;78:1035-44.
10. Longaker MA, Frieden IJ, LeBoit PE, Sherertz EF. Congenital "self-healing" Langerhans cell

histiocytosis: the need for long-term follow-up. J Am Acad Dermatol 1994;31:910-6.
11. Larralde M, Rositto A, Giardelli M, Gatti CF, Santos MA. Congenital self-healing histiocytosis (Hashimoto-Pritzker). Int J Dermatol 1999;38:693-6.
12. Jang KA, Ahn SJ, Choi JH, Sung KJ, Moon KC, Koh JK. Histiocytic disorders with spontaneous regression in infancy. Pediatr Dermatol 2000;17:364-8.
13. Hage C, Willman CL, Favara BE, Isaacson PG. Langerhans' cell histiocytosis (histiocytosis X): immunophenotype and growth fraction. Hum Pathol 1993;24:840-5.
14. Bank MI, Rengtved P, Carstensen H, Petersen BL. Langerhans cell histiocytosis: an evaluation of histopathological parameters, demonstration of proliferation by Ki-67 and mitotic bodies. APMIS 2003;111:300-8.
15. Ribalta T, McCutcheon IE, Aldape KD, Bruner JM, Fuller GN. The mitosis-specific antibody anti-phosphohistone-H3 (PHH3) facilitates rapid reliable grading of meningiomas according to WHO 2000 criteria. Am J Surg Pathol 2004;28:1532-6.
16. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. Pediatr Dermatol 2008;25:291-5.
17. Chu T, D'Angio GJ, Favara BE, Ladisch S, Nesbit M, Pritchard J. Histiocytosis syndromes in children. Lancet 1987;2:41-2.
18. Broadbent V, Gadner H, Komp DM, Ladisch S. Histiocytosis syndromes in children: II. Approach to the clinical and laboratory evaluation of children with Langerhans cell histiocytosis. Clinical Writing Group of the Histiocyte Society. Med Pediatr Oncol 1989;17:492-5.
19. Lau L, Krafchik B, Trebo MM, Weitzman S. Cutaneous Langerhans cell histiocytosis in children under one year. Pediatr Blood Cancer 2006;46:66-71.
20. Popadic S, Brasanac D, Arsov B, Nikolic M. Congenital self-healing histiocytosis presenting as blueberry muffin baby: a case report and literature review. Indian J Dermatol Venereol Leprol 2012;78:407.
21. Hansel K, Tramontana M, Troiani S, de Benedictis D, Bianchi L, Cucchia R, et al. Congenital self-healing Langerhans cell histiocytosis: A rare presentation of blueberry muffin baby "Spectrum". Dermatopathology (Basel) 2019;6:37-40.
22. Larralde M, Rositto A, Giardelli M, Gatti CF, Santos-Munoz A. Congenital self-healing Langerhans cell histiocytosis: the need for a long term follow up. Int J Dermatol 2003;42:245-6.
23. Titgemeyer C, Grois N, Minkov M, Flucher-Wolfram B, Gatterer-Menz I, Gadner H. Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. Med Pediatr Oncol 2001;37:108-14.
24. Battistella M, Fraitag S, Teillac DH, Brousse N, de Prost Y, Bodemer C. Neonatal and early infantile cutaneous langerhans cell histiocytosis: comparison of self-regressive and non-self-regressive forms. Arch Dermatol 2010;146:149-56.
25. Simko SJ, Garmezy B, Abhyankar H, Lupo PJ, Chakraborty R, Lim KP, et al. Differentiating skin-limited and multisystem Langerhans cell histiocytosis. J Pediatr 2014;165:990-6.
26. Larsen L, Merin MR, Konia T, Armstrong AW. Congenital self-healing reticulohistiocytosis: concern for a poor prognosis. Dermatol Online J 2012;18:2.
27. Esterly NB, Maurer HS, Gonzalez-Crussi F. Histiocytosis X: a seven-year experience at a children's hospital. J Am Acad Dermatol 1985;13:481-96.