Dermatopathology

Dermatopathology 2017;4:24–30
DOI: 10.1159/000481308
Published online: November 16, 2017

Case Studies

A 12-Month-Old Healthy Girl with a New Oral Ulcer and Chronic Diaper Rash

Hannah Song[a] Johanna S. Song[b] Elizabeth B. Wallace[b] Leonard B. Kaban[c] Mary S. Huang[d] Stefan Kraft[e] Martin C. Mihm Jr.[f] Daniela Kroshinsky[g]

[a]Harvard Medical School, [b]Harvard Combined Dermatology Residency Program, Departments of [c]Oral and Maxillofacial Surgery, [d]Pediatric Hematology-Oncology, and [e]Pathology, Massachusetts General Hospital, and Departments of [f]Pathology and [g]Dermatology, Brigham and Women's Hospital, Boston, MA, USA

Keywords
Langerhans cell histiocytosis · Histiocytic disorders · Diaper rash · Seborrheic dermatitis · Oral ulcer

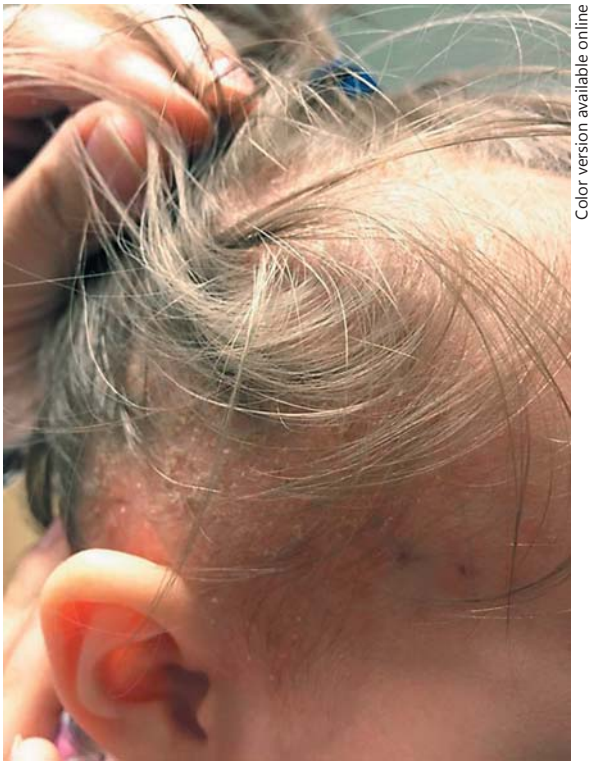
Abstract
A 12-month-old healthy girl presented with a chronic diaper rash. Physical examination demonstrated crusting of the scalp, erythematous papules with surrounding petechiae on the lower abdomen, and an intraoral palatal ulcer. Further imaging demonstrated bone involvement. Histopathologic examination of involved skin and the intraoral ulcer demonstrated epithelioid histiocytes with "coffee bean-shaped" nuclei, staining positive for CD1a and langerin by immunohistochemistry, consistent with Langerhans cell histiocytosis (LCH). LCH is a disease entity of unknown etiology characterized by histiocytic proliferation that most commonly presents in young children. The cutaneous findings of LCH include a seborrheic dermatitis-like and/or red-brown papular eruption. Intraoral examination is crucial as oral mucosal and maxillofacial skeletal disease can also be seen in LCH. When a child presents with a recalcitrant seborrheic dermatitis-like eruption or chronic diaper rash, the clinician should be alerted to the possibility of LCH. Timely recognition and diagnosis of LCH is important for oncologic referral, evaluation, and treatment.

Case Report

A 12-month-old healthy girl presented with a 3-month history of a nonhealing oral ulcer and chronic diaper rash. Dermatology was consulted for evaluation of a persistent diaper rash, which had not improved after months of topical steroid and antifungal treatments.

Daniela Kroshinsky, MD, MPH
Department of Dermatology, Massachusetts General Hospital
50 Staniford Street, 2nd Floor
Boston, MA 02114 (USA)
E-Mail dkroshinsky@partners.org

Dermatopathology 2017;4:24–30
DOI: 10.1159/000481308



Color version available online

Fig. 1. Thick, yellow crust on the temporal scalp. Photo: courtesy of Dr. Johanna S. Song.

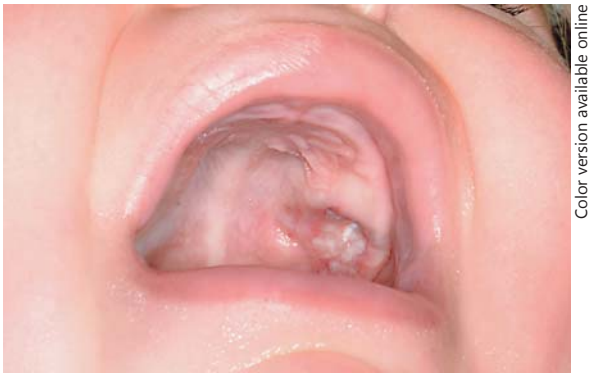
Physical examination demonstrated a thick, greasy, yellow adherent crust on the temporal scalp and behind both ears (Fig. 1). Intraoral examination demonstrated a 1.5-cm ulcerated lesion involving the left palatal mucosa (Fig. 2). There were multiple erythematous to violaceous nonblanching papules with a central hemorrhagic crust and surrounding petechiae present on the skin of the lower right abdomen (Fig. 3). Magnetic resonance imaging of the head revealed an enhancing lesion on the left palate in the area of the developing deciduous molar teeth and a 1.1-cm homogenous, enhancing intraosseous lesion within the right sphenoid triangle.

Biopsy specimens from the palatal lesion were received from the outside hospital and a 3-mm punch biopsy was performed on the right lower abdomen.

Diagnosis and Clinical Course

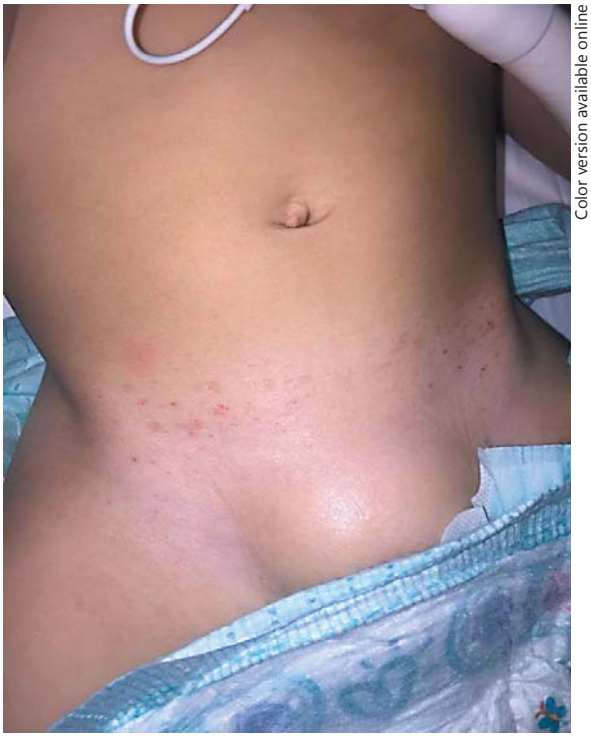
Histopathologic examination of the biopsy from the left palate ulcer demonstrated a submucosal monomorphic infiltrate composed of epithelioid cells with grooved, "coffee bean-shaped" nuclei. The epithelioid cells showed positive staining for CD1a and S100 by immunohistochemistry, consistent with a diagnosis of Langerhans cell histiocytosis (LCH) [1]. The erythematous papule on the right lower quadrant abdominal skin also showed a superficial dermal and focally intraepidermal infiltrate of epithelioid cells with admixed eosinophils (Fig. 4a, b). By immunohistochemistry, the epithelioid cells were strongly positive for CD1a, S100, and langerin (CD207) (Fig. 4c, d) and weakly positive for BRAFVE1. Molecular studies of the abdominal skin biopsy confirmed the presence of a BRAFV600E mutation. Magnetic resonance imaging of the head was consistent with bone involvement by LCH. The patient's presentation was consistent with multisystem LCH, and treatment

Dermatopathology 2017;4:24–30
DOI: 10.1159/000481308



Color version available online

Fig. 2. 1.5-cm ulcerated lesion involving the left palatal mucosa. Photo: courtesy of Dr. Leonard B. Kaban.



Color version available online

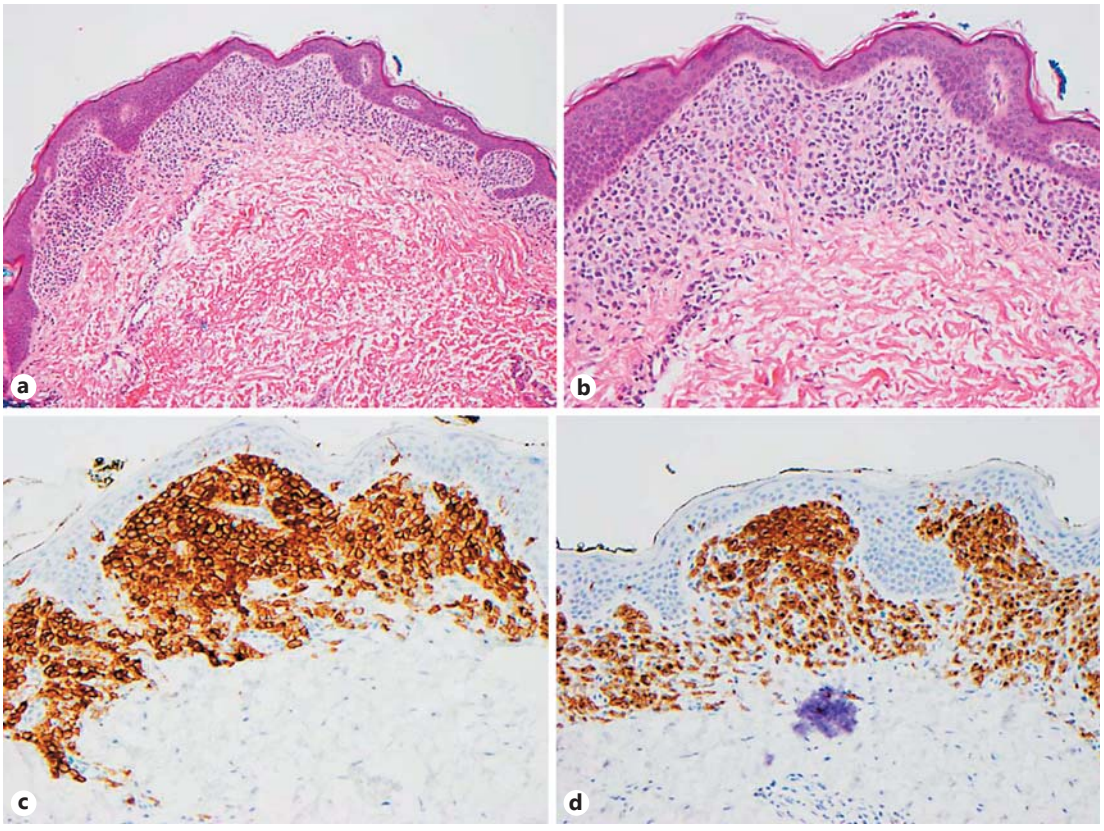
Fig. 3. Erythematous to violaceous nonblanching papules with central hemorrhagic crust and surrounding petechiae on the right abdomen. Photo: courtesy of Dr. Johanna S. Song.

was initiated with vinblastine and prednisone. The patient has completed 6 months of combination therapy with interval improvement in both the intraoral mass and cutaneous eruption.

Discussion

LCH is a disease entity characterized by a cellular proliferation that most commonly presents in children 0–3 years old. This rare disease has an incidence of only 0.5–5.4 cases per million persons per year but represents the most common histiocytic disorder [2–4]. The etiology of LCH is poorly understood. Two leading theories regarding the mechanism of LCH include that it is (1) a dysfunctional immune response and (2) a clonal neoplastic process [5]. While some features of the disease, such as increased cytokine levels in tissue samples and

Dermatopathology 2017;4:24–30
DOI: 10.1159/000481308



Color version available online

Fig. 4. a Superficial dermal mononuclear infiltrate (HE, original magnification ×10). **b** Superficial dermal histiocytic infiltrate with eosinophils (HE, original magnification ×20). **c** Positive immunohistochemical staining for CD1a (original magnification ×20). **d** Positive immunohistochemical staining for langerin (original magnification ×20).

an occasionally benign disease course, seem to suggest an inflammatory process, other findings, such as the monoclonal nature of the cells and characteristic mutations in BRAFV600E and MAP2K1, are supportive of a clonal neoplastic process [6–8].

The current classification system of LCH stratifies disease by organ involvement into single-system and multiple-system LCH [9, 10]. Single-system disease usually targets the bone, especially the skull, followed by long and flat bones. The second most commonly affected organ is the skin, representing 10% of single-system LCH involvement [11]. Multi-system LCH commonly affects the bone and skin, but other potential organs of involvement include the lymph nodes, bone marrow, lungs, liver, spleen, pituitary gland, and central nervous system [10].

The cutaneous findings of LCH include a seborrheic dermatitis-like and/or red-brown papular eruption. The seborrheic dermatitis-like eruption often manifests on the scalp, flexural neck, axilla, trunk, and perineum [12]. Compared to seborrheic dermatitis, LCH may have discrete papules on close examination. Furthermore, patients will fail conventional treatments for seborrheic dermatitis and have a persistent rash. On the trunk and extremities, there may be red-brown papules accompanied by erosion, crusting, and petechial or purpuric changes. Our patient presented with these classic findings, including seborrheic dermatitis-like eruption on the scalp, as well as small erythematous papules and petechiae on the trunk. Atypical vesiculopustular, molluscum-like, and “blueberry muffin” presenta-

tions have also been reported in neonates [13, 14]. Though these features were not present in our patient, LCH should be considered in a child with a diffuse rash and systemic symptoms, such as fevers and lymphadenopathy.

Given the possibility of oral mucosal and maxillofacial skeletal disease, a thorough intraoral examination is crucial when considering a diagnosis of LCH. Painful ulcers or masses, as well as either premature eruption or loss of teeth, are all potential intraoral manifestations of LCH [15, 16]. Radiographs may demonstrate diffuse bone destruction with the premature eruption, loosening, or loss of teeth. Oral mucosal involvement can lead to pain, poor feeding, and decreased oral function and may significantly impact quality of life [17, 18].

Characteristic histopathologic findings for LCH include a mononuclear cell infiltrate in the papillary dermis, sometimes also in the epidermis, and rarely in the reticular dermis, with a variable inflammatory infiltrate. Scattered eosinophils can be a common finding. The mononuclear cells are epithelioid with a nucleus that has a deep groove, often likened to a kidney bean. Immunohistochemistry demonstrates positive staining of the epithelioid cells for CD1a, langerin (CD207), and S100 and can help distinguish LCH from other histiocytic disorders [19, 20]. The neoplastic cells have an immunophenotype similar to Langerhans cells but are thought to be possibly immature Langerhans cells or possibly dendritic cells.

Timely recognition and diagnosis of LCH is important for oncologic evaluation and treatment. Initial evaluation includes basic laboratory tests and biopsy for histopathologic diagnosis. This is taken from the most easily accessible involved organ and is usually the bone or skin. Based on the initial test results, hematology-oncology may pursue further studies, including biopsy of the bone marrow, lung, or liver and computed tomography/magnetic resonance imaging to determine the extent of disease [21].

Treatment for LCH is dependent on disease severity. If there is no systemic involvement, isolated cutaneous disease can be managed with topical steroids. Second-line treatments include topical tacrolimus, nitrogen mustard, imiquimod, narrowband ultraviolet B radiation, and psoralen and ultraviolet A radiation [5]. However, in pediatric patients, psoralen and ultraviolet A radiation should not be used due to increased risk for secondary malignancies [22–24]. Systemic treatment is reserved for patients with multisystem disease. One-year combination therapy with mercaptopurine, vinblastine, and prednisone is superior to shorter courses of treatment [25]. Initial success has been reported with the BRAF inhibitor vemurafenib for LCH with BRAFV600E mutations [26].

The prognosis of LCH depends on a variety of factors, including age, number of involved organs, and initial treatment response. Young patients who are less than 2 years of age can present with more acute, disseminated disease. While the vast majority of patients with isolated cutaneous findings have progression-free survival at 3 years, less than half of the patients with multisystem disease are in remission at 3 years [10, 11, 27]. Notably, "high-risk" organ involvement, specifically of the hematopoietic system, central nervous system, liver, and spleen, portends a poor prognosis [28]. The failure to respond to initial chemotherapy after the initial 6–12 weeks of treatment is also a poor prognostic marker [10]. Our patient has several risk factors for poor prognosis, including an age younger than 2 years at initial presentation and multisystem disease. However, she lacks "high-risk" organ involvement and has exhibited initial response to treatment. Long-term, close clinical follow-up is required in all patients with single- and multi-system disease, given the possibility of progression to systemic disease and/or relapse after remission.

This case highlights the fundamental concepts in the diagnosis, treatment, and management of LCH, a condition that most commonly presents in young children. When a child presents with a recalcitrant seborrheic dermatitis-like eruption or chronic diaper rash, the clinician should be alerted to the possibility of LCH to prevent a delay in diagnosis and treatment.

Statement of Ethics

The manuscript was prepared in compliance with all ethical and confidentiality guidelines and principles.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Satter EK, High WA: Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. Pediatr Dermatol 2008;25:291–295.
2 Egeler RM, D'Angio GJ: Langerhans cell histiocytosis. J Pediatr 1995;127:1–11.
3 Weitzman S, Egeler RM: Langerhans cell histiocytosis: update for the pediatrician. Curr Opin Pediatr 2008;20:23–29.
4 LCH in Children – Histiocytosis Association. http://www.histio.org/lchinchildren#.WIYmYrYrJAY (accessed January 23, 2017).
5 Abla O, Egeler RM, Weitzman S: Langerhans cell histiocytosis: current concepts and treatments. Cancer Treat Rev 2010;36:354–359.
6 de Graaf JH, Tamminga RY, Dam-Meiring A, Kamps WA, Timens W: The presence of cytokines in Langerhans' cell histiocytosis. J Pathol 1996;180:400–406.
7 Badalian-Very G, Vergilio J-A, Degar BA, et al: Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116:1919–1923.
8 Zeng K, Ohshima K, Liu Y, et al: BRAFV600E and MAP2K1 mutations in Langerhans cell histiocytosis occur predominantly in children. Hematol Oncol 2016, DOI: 10.1002/hon.2344.
9 Emile J-F, Abla O, Fraitag S, et al: Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 2016;127:2672–2681.
10 Simko SJ, Garmezy B, Abhyankar H, et al: Differentiating skin-limited and multisystem Langerhans cell histiocytosis. J Pediatr 2014;165:990–996.
11 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;37:108–114.
12 Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ: Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer 1999;85:2278–2290.
13 Huang JT, Mantagos J, Kapoor R, Schmidt B, Maguiness S: Langerhans cell histiocytosis mimicking molluscum contagiosum. J Am Acad Dermatol 2012;67:e117–e118.
14 Gee SN, Huang JT, Schmidt BA, Gellis SE: Rapidly fatal multiorgan Langerhans cell histiocytosis in a neonate. Pediatr Dermatol 2013;30:e85–e86.
15 Jalil ABA, Hin-Lau S: Oral Langerhans cell histiocytosis in Malaysian children: a 40-year experience. Int J Paediatr Dent 2009;19:349–353.
16 Madrigal-Martínez-Pereda C, Guerrero-Rodríguez V, Guisado-Moya B, Meniz-García C: Langerhans cell histiocytosis: literature review and descriptive analysis of oral manifestations. Med Oral Patol Oral Cir Bucal 2009;14:E222–E228.
17 Chuong R, Kaban LB: Diagnosis and treatment of jaw tumors in children. J Oral Maxillofac Surg 1985;43:323–332.
18 Troulis MJ, Williams WB, Kaban LB: Jaw Tumors in Children. Pediatric Oral and Maxillofacial Surgery. Philadelphia, WB Saunders, 2004.
19 Sholl LM, Hornick JL, Pinkus JL, Pinkus GS, Padera RF: Immunohistochemical analysis of langerin in Langerhans cell histiocytosis and pulmonary inflammatory and infectious diseases. Am J Surg Pathol 2007;31:947–952.
20 Histiocytic and Dendritic Cell Neoplasms Including Langerhans Cell Histiocytosis and Langerhans Cell Sarcoma – ClinicalKey. https://www-clinicalkey-com.ezp-prod1.hul.harvard.edu/#!/content/book/3-s2.0-B9780323296137000533?scrollTo=%23s0010 (accessed September 14, 2016).
21 Haupt R, Minkov M, Astigarraga I, et al: Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer 2013;60:175–184.
22 Stern R: Metastatic squamous cell cancer after psoralen photochemotherapy. Lancet 1994;344:1644–1645.
23 Stern RS, Nichols KT: Therapy with orally administered methoxsalen and ultraviolet A radiation during childhood increases the risk of basal cell carcinoma. The PUVA Follow-up Study. J Pediatr 1996;129:915–917.

24 Stern RS, Nichols KT, Väkevä LH: Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study. N Engl J Med 1997;336:1041–1045.

25 Gadner H, Grois N, Pötschger U, et al: Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood 2008;111:2556–2562.

26 Hyman DM, Puzanov I, Subbiah V, et al: Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373:726–736.

27 Ehrhardt MJ, Humphrey SR, Kelly ME, Chiu YE, Galbraith SS: The natural history of skin-limited Langerhans cell histiocytosis: a single-institution experience. J Pediatr Hematol Oncol 2014;36:613–616.

28 Minkov M: Multisystem Langerhans cell histiocytosis in children: current treatment and future directions. Paediatr Drugs 2011;13:75–86.