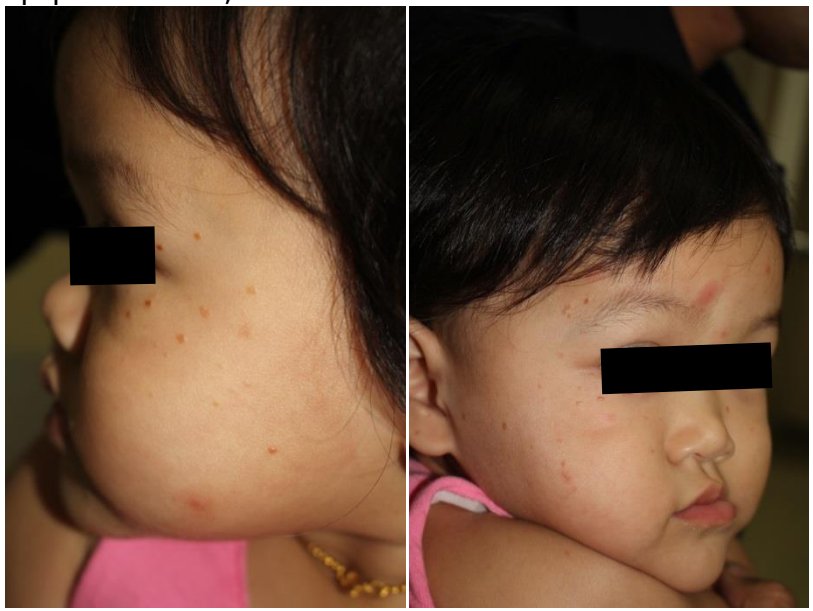
Case 11

A 1-year-old Thai girl from Bangkok

Chief complaint: Multiple asymptomatic yellowish-brownish papules on face, trunk and extremities for 2 months



Present illness: The patient developed multiple, small, asymptomatic, discrete yellowish-brown papules on face, trunk and extremities for 2 months. The lesions are predominately located on face, particularly in periorbital region. She was treated with 2% hydrocortisone cream with partially response.

Past history: She had been diagnosed with unknown cause neonatal seizure since she was 1 month old. Her symptom was well controlled with phenobarbital and the patient was able to stop her medication by 5 months of age. Her growth and development profile are unremarkable.

Physical examination

A Thai girl, active

HEENT: Not pale conjunctiva, anicteric sclera

Lymph node: Not palpable

CVS: Normal S1 S2, no murmur

Lung: Clear

Abdomen: No hepatosplenomegaly

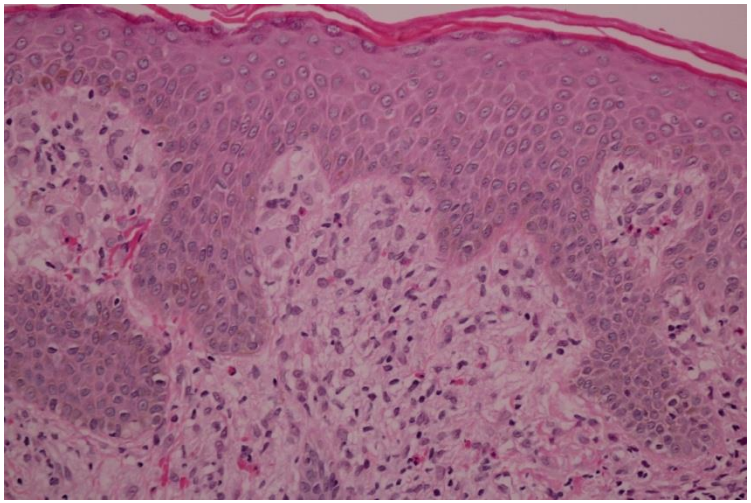
Growth and development: WNL

Skin examination

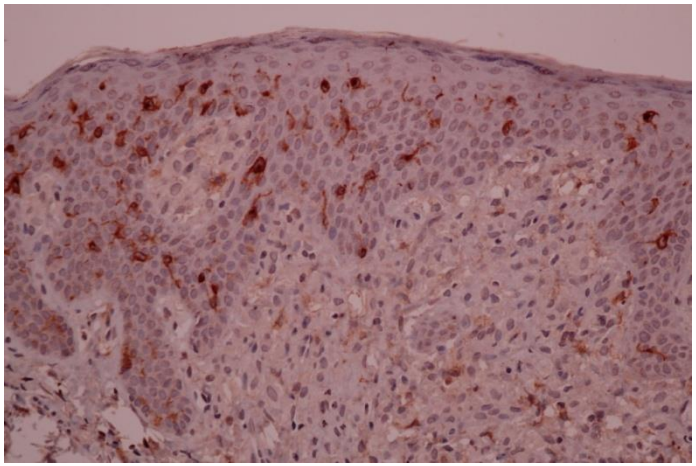
Multiple discrete yellowish-brown papules on face, trunk and extremities

Histopathology (S15-001940, trunk)

- Dense lichenoid inflammatory cell infiltrate of lymphocytes, histiocytes, eosinophils, extravasated erythrocytes admixed with some langerhans cell in the papillary dermis
- Langerhans cells, characterized by, bean-shaped eccentrically located nuclei and abundant pale eosinophilic cytoplasm.
- Mild epidermal hyperplasia



Immunohistochemistry stain (S15-24593, trunk)
Langerhans cells: positive for CD1a



Investigation
CBC, LFT, Renal function: WNL
LDH: 255 U/L
Ultrasound whole abdomen: No hepatosplenomegaly
Bone marrow biopsy: Normocellular bone marrow showing adequate trilinear hematopoiesis
Film bone survey: No osteolytic lesion

Diagnosis: Cutaneous langerhans cell histiocytosis

Treatment: 0.03% Tacrolimus ointment apply lesion twice daily

Presenter: Ruedee Phasukthaworn, MD

Consultant: Tueboon Sriphojanart, MD

Discussion:

Langerhans cell histiocytosis (LCH) is a heterogeneous disease, characterized by accumulation of dendritic cells with features similar to epidermal Langerhans cells in various organs. LCH is more frequently involved in skeleton, skin and pituitary gland. Other less common involved organs are liver, spleen, hematopoietic system, lungs and lymph nodes.

LCH is believed to affect fewer than 1 in 200,000 children; however, any age group can be affected.[1] There are other terms for LCH include histiocytosis X, eosinophilic granuloma, Letterer–Siwe disease, and Hand–Schüller–Christian disease. However the current nomenclature classified LCH into either single or multiorgan involvement, which can informs disease extent and prognosis as described in table 1.[2, 3]

The true pathogenesis of LCH is remaining unidentified, whether the clonal proliferation of LCH cells are results from a malignant transformation or an immunological stimulus. However neoplastic origin of LCH has been suggested due to the detection of the mutually exclusive activating somatic BRAF V600E and MAP2K1 gene mutations that occur in about 75% of patients.[4-6]

Table 1: Classification of Langerhans-Cell Histiocytosis	
Single-system Disease	
Localized (single site)	Monostotic bone involvement Isolated skin involvement Solitary lymph node involvement
Multiple site	Polyostotic bone involvement Multifocal bone disease involvement Multiple lymph node involvement
Multi-system Disease	
Low-risk group	Disseminated disease with involvement of low-risk organs (skin, bone, lymph node, pituitary)
High-risk group	Disseminated disease with involvement of one or more of the high-risk organs (hematopoietic system, lungs, liver, and spleen)

Cutaneous manifestations in LCH are common and may represent the initial sign of the disease. The typical lesion is small translucent rose-yellow papule predominately on trunk and scalp. Vesicles and pustules are common skin finding especially in neonatal period. Extensive papuloscaling and papulocrusted patches can be found and mimicked seborrheic dermatitis. The finding of purpura is a sign of poor prognosis. Mucosal lesion is also common finding, presents with noduloulcerative lesion on oral and genital area.

To prove the diagnosis of LCH, positive immunostaining for CD1a, S100 and Langerin or demonstration of Birbeck granules on electron microscopy are required. LCH patients should undergo investigation for hematologic, pulmonary, hepatosplenic, renal, and skeletal involvement to determine the extent of disease.

The prognosis of patients with LCH is varies, range from mild or asymptomatic course to aggressive multiple organ involvement with fatality. The high mortality rate is found in patient with multisystem disease, especially in children less than 2 years of age, and in any patient with hematopoietic system, liver, lungs or spleen involvement.

The treatment of LCH depends on disease severity and organ involvement. Topical corticosteroid, tacrolimus, imiquimod and phototherapy (NBUVB, PUVA) have been reported to be effective in mild single system skin involvement.[7, 8] For more extensive cutaneous disease, thalidomide may be effective.[9] Systemic corticosteroid and antimitotic drug are indicated in resistant limited skin disease. Surgery is the treatment of choice for bone involvement.

For multiorgan involvement LCH, chemotherapy is indicated. Currently, monochemotherapy with vinblastine with or without glucocorticoid is the most proper management.[10] For the patients who failed from monochemotherapy, multiagent regimens including vincristine, cyclophosphamide, doxorubicin, and chlorambucil may be considered. Therefore, the recent detection of mutations in BRAF and MAP2K1 genes in LCH patients could transform the conventional therapy to targeted therapy in the near future.

In our patient, she has mild limited cutaneous involvement LCH. Therefore, she has been treated with topical tacrolimus ointment with partially response.

References

1. Arceci RJ. The histiocytoses: the fall of the Tower of Babel. Eur J Cancer (Oxford, England : 1990) 1999;35:747-67; discussion 67-9.
2. Favara BE, Feller AC, Pauli M, Jaffe ES, Weiss LM, Arico M et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol1997;29:157-66.
3. Satter EK , High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. Pediatr Dermatol2008;25:291-5.
4. Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116:1919-23.
5. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949-54.
6. Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. Blood 2014;124:1655-8.
7. Rieker J, Hengge U, Ruzicka T , Bruch-Gerharz D. [Multifocal facial eosinophilic granuloma: successful treatment with topical tacrolimus]. Hautarzt2006;57:324-6.
8. Taverna JA, Stefanato CM, Wax FD , Demierre MF. Adult cutaneous Langerhans cell histiocytosis responsive to topical imiquimod. J Am Acad Dermatol2006;54:911-3.
9. McClain KL , Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. Pediatr Blood Cancer2007;48:44-9.
10. Weitzman S, Braier J, Donadieu J, Egeler RM, Grois N, Ladisch S et al. 2'-Chlorodeoxyadenosine (2-CdA) as salvage therapy for Langerhans cell histiocytosis (LCH). results of the LCH-S-98 protocol of the Histiocyte Society. Pediatr Blood Cancer2009;53:1271-6.