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ORIGINAL ARTICLE

Diverse cutaneous manifestation of Langerhans cell histiocytosis: a 10-year retrospective cohort study

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Abstract

Cutaneous manifestation is a common presentation of LCH and is usually a leading clue for the disease diagnosis. Having cutaneous lesions did not show a significantly early age onset at diagnosis compared to those without skin lesions, *P* value = 0.71. In the present study, cutaneous findings were found as 77.7%. Seborrheic dermatitis-like lesions were the most common cutaneous type (42.8%), followed by papules/nodules/masses (28.5%), petechiae/hemorrhagic lesions (17.8%), and eczematous lesions (10.7%). Time to diagnosis of LCH presented with seborrheic dermatitis-like lesions was significantly longer than other cutaneous presentations, *P* value = 0.0011.

Conclusion: Patients with LCH who had the manifestations of seborrheic dermatitis-like lesions can have diagnosis delayed due to the difficulty in distinguishing these lesions from normal seborrheic dermatitis lesions. Petechiae/hemorrhagic cutaneous signs in addition to the normal seborrheic dermatitis is the clue for early detection of the disease. To improve early detection of LCH, general pediatricians should be alerted to be aware of these skin symptoms, and if they persist, a dermatologist, pediatric if available, should be immediately consulted.

What is Known?

- *Cutaneous manifestation is a common presentation of LCH and is usually a leading clue for the disease diagnosis.*

What is New?

- *Patients with LCH who have the manifestations of seborrheic dermatitis-like lesions can have a delayed diagnosis due to the difficulty in distinguishing normal from seborrheic dermatitis lesions.*
- *Petechiae/hemorrhagic cutaneous signs in addition to the normal seborrheic dermatitis are the clue to the early disease detection.*

Keywords Langerhans cell histiocytosis · LCH · Seborrheic dermatitis · Petechiae · Hemorrhagic lesions

Abbreviations

LCH	Langerhans cell histiocytosis
S-S LCH	Single-system Langerhans cell histiocytosis
M-S LCH	Multisystem Langerhans cell histiocytosis

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Introduction

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorders [1–3]. It has an estimated incidence of approximately two to nine cases per million children per year, peaks between 1 and 4 years of age, and has a slight predominance in males [3–6]. Adult onset is less frequent, and the average number is less than 30% of cases [7, 8]. The disease is characterized by presentation of aberrant functions, differentiation, and/or proliferation of cells of the mononuclear phagocyte system [8, 9]. These types of cells can arise in various tissues, but the common locations are skin, bone [10], lymph nodes [11], the lungs, and the pituitary [11–13]. Thus, patients with LCH demonstrate a variety of clinical presentations among these involved in several organ systems. This variety also indicates

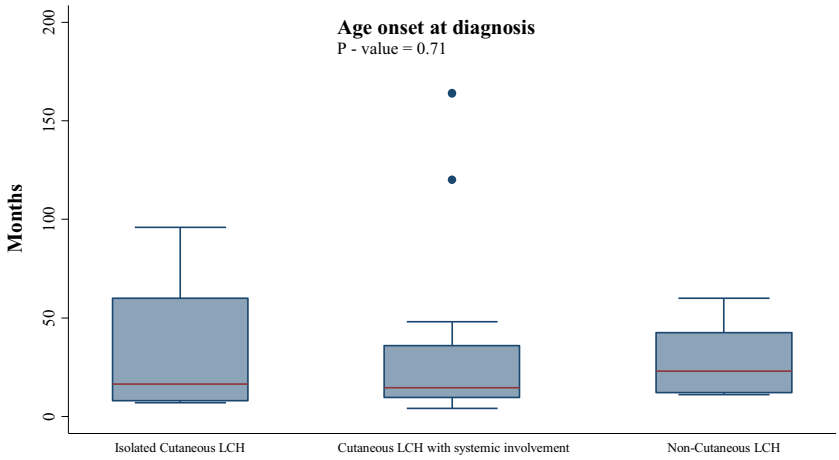

Fig. 1 Age of onset at diagnosis of LCH in the study population. Patients are divided into (i) isolated cutaneous LCH, (ii) cutaneous LCH with systemic involvement, and (iii) non-cutaneous LCH. Red lines show median age

the different possible outcomes [14]. Patients with "single-system" LCH (S-S LCH)—single organ/system involvement—tend to have more favorable outcomes compared to "Multisystem" LCH (M-S LCH) involvement of two or more organs at diagnosis, with or without involvement/dysfunction of "risk organs," e.g., the hematopoietic system, involving liver and/or spleen [15]. This classification is based on a stratification system developed by The Reclassification Working Group of the Histiocyte Society [16].

The cutaneous manifestation is a common presentation of LCH and is usually a leading clue for disease diagnosis [5, 17]. A number of LCH cases during the past 10 years at a tertiary care pediatric referral center, Pediatric Department, Faculty of Medicine, Khon Kaen University, Thailand, were reviewed. The authors found a large number of LCH patients in the institute compared to previous studies. Furthermore, some LCH patients had delayed diagnosis due to undiagnosed of cutaneous lesions. Most residents and general pediatricians were and are still unable to detect the pattern of abnormal findings which may be the lead clue for LCH diagnosis. Thus, the authors gathered all the clinical presentations and disease courses of children with LCH, and focused on the patients with cutaneous findings, and these data were analyzed statistically in order to find significant cutaneous findings of awareness in LCH.

Methods

Data collection

Retrospective chart reviews were performed on all diagnosed LCH patients at the tertiary care pediatric referral center, Pediatric Department, Faculty of Medicine, Khon Kaen University, Thailand, between January 2008 and December 2017. The diagnosis of LCH was confirmed by histological and immunohistochemical stains (S100 and CD1a).

Statistical methods

At the end of the study, the collected data were analyzed using STATA software version 10 (StataCorp LP). Descriptive statistical methods—means, standard deviations (SDs), medians, and frequencies—were used to analyze the demographic data. Comparisons of categorical variables among the groups were performed using a chi-square and Mann-Whitney *U* tests. The Kruskal-Wallis

Table 1 Comparison of LCH patients' characteristics distributed between isolated cutaneous LCH, cutaneous LCH with systemic involvement, and non-cutaneous LCH

Variable	Isolated cutaneous LCH ($n = 4$)	Cutaneous LCH with systemic involvement ($n = 24$)	Non-cutaneous LCH ($n = 8$)	Statistics
Patient sex				
Male	1	11	3	
Female	3	13	5	
Onset of eruption				Chi-square: P value = 0.22
≤ 12 months	2	11	3	
> 12 months	2	13	5	
Age at onset (months) (min–max)	16.5 (7–96)	14.5 (4–164)	23 (11–60)	Kruskal-Wallis test: P value = 0.71

Table 2 Types of cutaneous lesions and time to diagnosis

Type of cutaneous lesion	*N*	Time to diagnosis (min–max) (months)	Statistics
Seborrheic dermatitis-like lesions	12	12 (2–24)	*P* value = 0.0011
Papules/nodules/masses	8	2.5 (1–12)	
Petechiae/hemorrhagic lesions	5	0.5 (0.4–1)	
Eczematous lesions	3	7 (5–8)	

test was used to analyze multiple comparisons of categorical variables. Values of $P < 0.05$ were considered to indicate statistical significance.

Results

There were a total of 36 LCH patients during the study period. Four patients were diagnosed as S-S LCH by manifestation of isolated cutaneous lesions, and 32 were M-S LCH. There were 15 boys and 21 girls. The patients were 4 months to 13 years of age at the time of diagnosis.

The authors also classified patients in to three groups aimed to focus on cutaneous lesions as follows: (i) isolated cutaneous lesions (4 out of 36), (ii) cutaneous lesions with systemic involvement (24 out of 36), and (iii) non-cutaneous lesions (8 out of 36). Median ages at diagnosis of each group were 16.5 months, 14.5 months, and 23 months. LCH patients with cutaneous presentations showed an earlier age onset at diagnosis compared to non-cutaneous LCH; however, no significant statistical differences were seen, *P* value = 0.71 (Fig. 1). Table 1 shows patient sexes and ages onset in each group at diagnosis.

Presenting symptoms and lesions of LCH patients in the study population included cutaneous lesions, hepatosplenomegaly, otitis media, lymphadenopathy, prolonged fever, exophthalmos, gum hypertrophy, anemia, thrombocytopenia, bone pain, and polyuria from diabetes insipidus (DI).

Cutaneous lesions were the most common manifestation found in the study population (28 out of 36 cases, 77.7%). Other lesions involving organs that were in the study population included bone (46%), lymph node (37%), liver/spleen (34%), bone marrow (25%), and pituitary (15%).

Various cutaneous lesions were documented in the study population. They were seborrheic dermatitis-like lesions (12 of 28, 42.9%), followed by solitary papules/nodules and masses (8 of 28, 28.6%), petechiae/hemorrhagic lesions (5 of 28, 17.8%), and eczematous lesions (3 of 28, 10.7%). Significant median differences of time to diagnosis were noted among the different cutaneous groups. Petechiae/hemorrhagic lesions showed the shortest timing to diagnosis, while seborrheic dermatitis-like lesions showed the longest timing to diagnosis (Kruskal-Wallis test, *P* value = 0.0012). Table 2 represents time to diagnosis among different cutaneous lesions in the study population. Mann-Whitney *U* test was used to analyze multiple comparisons of time to diagnosis of each cutaneous type as presented in Fig. 2. The most common site involved on the skin was the scalp (10 of 28 cases), followed by the trunk (4 of 28 cases) and diaper area (4 of 28 cases).

Two patients who presented with isolated cutaneous lesions without other organ involvement were treated as atopic

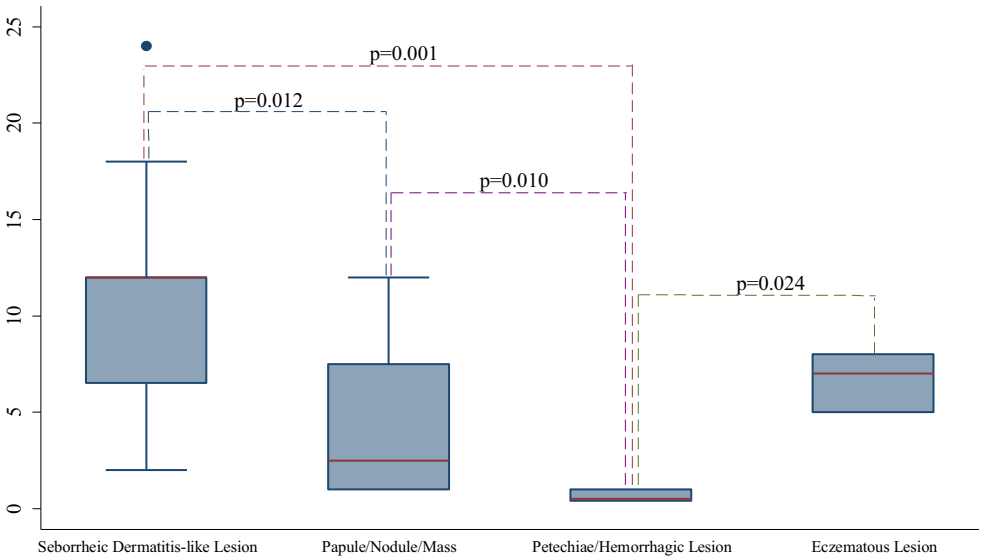

Fig. 2 Boxplot graph represents time to diagnosis of LCH among the different cutaneous types in the study population. Red line shows median time in months. Seborrheic dermatitis-like lesion shows the longest time to diagnosis compared to other cutaneous types

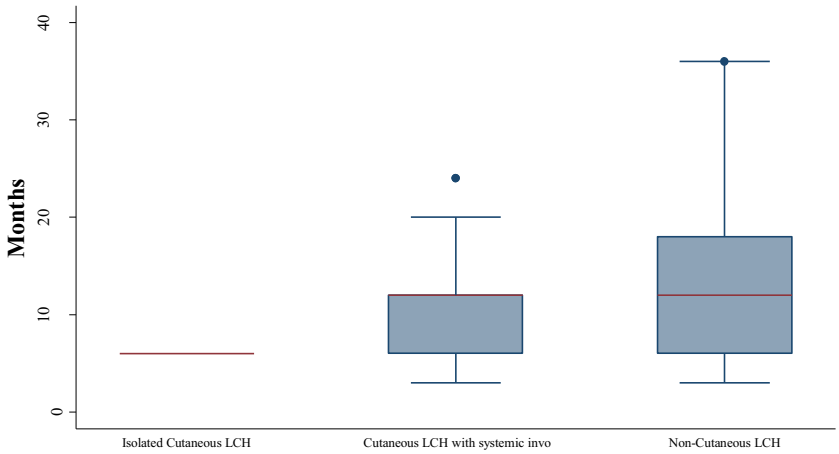

Fig. 3 Boxplot graph represents time to remission of LCH in the study population. Patients are divided into (i) isolated cutaneous LCH, (ii) cutaneous LCH with systemic involvement, and (iii) non-cutaneous LCH. Red lines show median ages (*P* value = 0.15)

dermatitis for 8 months before pathological diagnoses of LCH from skin biopsies were made.

Confirmations of the diagnosis of all patients were of LCH by histology of tissues and immunohistochemical stains. The tissue biopsy sites (skin, bone, lymph node, bone marrow) were varied and depended on individual presenting symptoms of patients. Most frequent tissue biopsy site was skin (22 cases, 55.5%), followed by bone (5 cases, 13.8%), lymph node (4 cases, 11.1%), bone marrow (4 cases, 11.1%), and pericardial fluid (1 case, 2.7%).

Vinblastine as mono-therapy and/or combined with other medications was the most frequent chemotherapy used in the study population (30 cases, 83.3%), followed by prednisolone combined with other chemotherapy (5 cases, 13.8%), mercaptopurine (5 cases, 13.8%), methotrexate (2 cases, 5.5%), cytosine arabinoside (2 cases, 5.5%), and etoposide (1 case, 2.7%). The treatment depended on clinical presentation of S-S LCH or M-S LCH. The first line of treatment was using vinblastine as mono-therapy for S-S LCH, while other chemotherapies were added if the clinical presentation was M-S LCH or if there was no response to the mono-therapy regimen. The median follow-up duration was 17 months (3 months–72 months). Eight patients were lost to follow-up after 12 months; however, all patients were still alive and in complete remission at the time of the last review.

Discussion

LCH is a rare neoplastic disease characterized by presenting of aberrant functions, differentiation, and/or proliferation of cells of the mononuclear phagocyte system [18]. This type of cells can arise in various tissues, but the common locations are skin, bone, lymph nodes, the lungs, and the pituitary [11–13]. Recently, a novel understanding of LCH has led to the concept of a true Langerhans cell neoplasia [8] after the improved genomic technology heralded a breakthrough in LCH biology and frequent mutations in BRAF V600E have been found in LCH specimens [9, 19–21]. Common mutations in various histiocytic populations of diverse ontogeny and at different

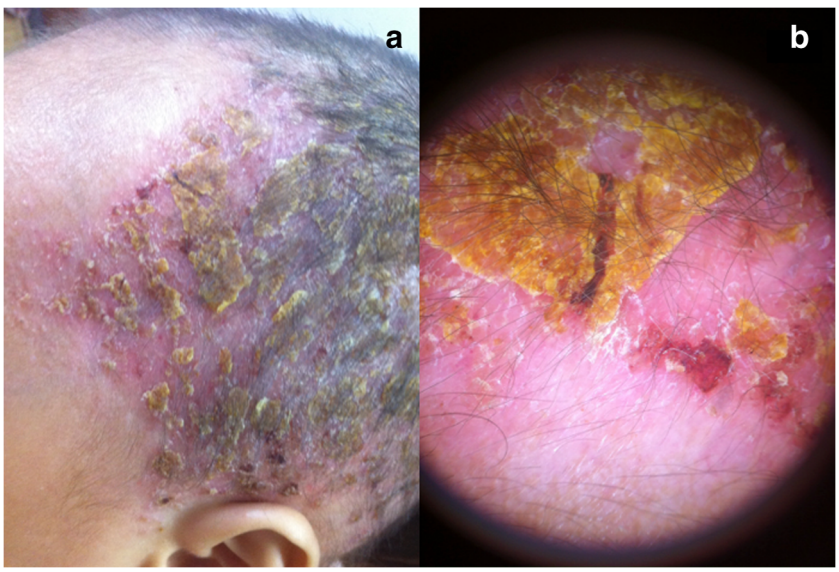

Fig. 4 Seborrheic dermatitis-like lesion on the scalp (**4A**) and petechiae/hemorrhagic crusts were observed under dermoscope examination on the presenting involved area (**4B**)

stages of differentiation may be responsible for the diverse clinical picture of this neoplastic entity. Therefore, various clinical presentations of LCH can be found according to various originating tissues.

The cutaneous manifestation has been documented to be the most common finding of LCH in many studies [3–5, 7, 22]. Similar to the present data, the cutaneous findings were as high as 77.7% among the study population. LCH patients who had skin presentations tended to have an onset at diagnosis at an age earlier than without cutaneous findings. From the present study, however, statistical significance of age at onset of diagnosis was not found between groups with and without cutaneous presentation, P value = 0.71. This non-significance may be explained by a limitation of the small numbers of the patients without cutaneous lesions.

Seborrheic dermatitis-like lesions have been noted to be one of the common finding in LCH patients [3, 4, 7]. These data are correlated to the present study in that seborrheic dermatitis-like lesions were the most common cutaneous findings found in the study population (12 of 28, 42.9%). Interestingly, this cutaneous type was also the one that had the longest time to diagnosis (median time to diagnosis = 12 months) compared to other types of cutaneous presentation, P value = 0.0012 (Fig. 3). This may be explained by the fact that seborrheic dermatitis is the common finding that is usually seen during childhood. Common presentation of seborrheic dermatitis is thus hard for the general pediatrician to distinguish between the normal and abnormal one. According to these difficult distinguishing characteristics, delayed diagnoses of LCH from these cutaneous findings were relatively high. This presenting point should be noted for generating in a part of LCH diagnosis awareness.

The eczematous lesion was also the cutaneous finding that had a longer time to diagnosis compared to other skin finding type (Fig. 3). In the current study, two patients were treated as atopic dermatitis for 8 months before being diagnosed with LCH. This may be explained by the reason as how to seborrheic dermatitis-like lesions are displayed.

Petechiae/hemorrhagic lesions were a less frequent finding but had the shortest time to diagnosis (Fig. 3). This finding fulfills a warning sign to suspect an abnormal manifestation since in normal seborrheic dermatitis and eczematous lesions are usually not presented by bleeding points in the involved area (Figs. 4 and 5).

The therapeutic options, skin-directed, topical application therapies [23] are the first choice in limited disease, while systemic chemotherapy has traditionally been used in extensive disease. In the study, all patients received systemic chemotherapy. In limited disease of isolated cutaneous LCH, skin-directed therapies were applied in combination with systemic chemotherapy.

The overall prognosis of LCH patients in the study population was good in all group classifications: S-S LCH, M-S LCH, isolated cutaneous LCH, cutaneous with systemic involvement, and non-cutaneous LCH. Even though eight patients lost to follow-up after 12 months, all patients were still alive and in complete remission at the time of last review. Median time to remission between isolated cutaneous LCH, cutaneous with systemic involvement, and non-cutaneous LCH was analyzed; however, no statistical differences in time of remission between groups were seen, P value = 0.15 (Fig. 4) (Supplement file).

The main limitations of this study were a small sample size of LCH patients and the retrospective cohort study design that caused missing of some unrecorded data. Some LCH patients with cutaneous lesions did not undergo skin biopsy; thus, the authors cannot prove that those children without skin histology had such a normal skin lesion or the pathologic LCH cutaneous lesion. However, when the authors looked back in details of each patient, we found out that six patients with cutaneous lesions and whom did not have skin histology were presented with a cutaneous mass (table in supplement file). All of them were confirmed diagnoses with lymph node biopsies and one patient with pericardial fluid histology. None of them were documented to have seborrheic dermatitis or any other cutaneous lesions that mimic 'normal' cutaneous presentation in children.

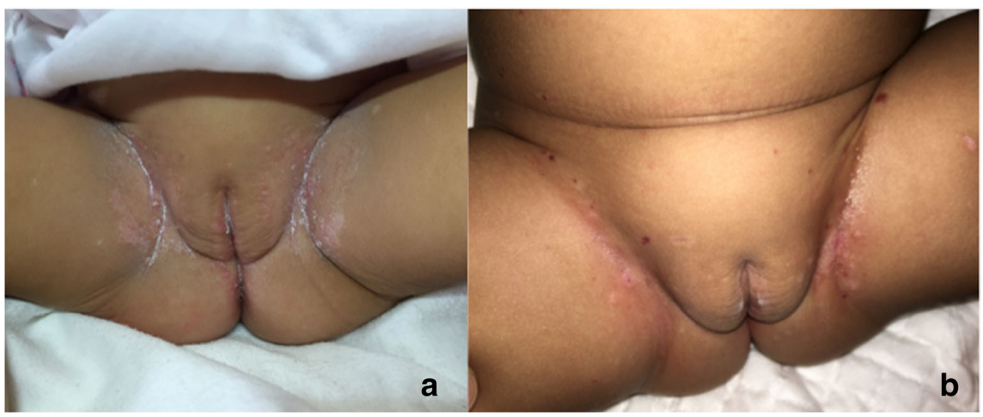

Fig. 5 Seborrheic dermatitis-like lesion on the diaper area. Panels **5A** and **5B** were taken from the same patient in the different time. LCH was diagnosed when petechiae/hemorrhagic lesions on **5B** were revealed

In summary, cutaneous manifestations are common among LCH patients. These presentations are usually the diagnostic clues for the disease diagnosis; however, some cutaneous manifestations can mimic other common skin findings in children, especially seborrheic dermatitis-like lesions which were the most common skin type in LCH but had a longest time to diagnosis in the study population. The clinical clue is to look for abnormal specific cutaneous findings such as petechiae/hemorrhagic lesions. If any presenting signs like petechiae/hemorrhagic lesions are found in addition, performing further skin biopsies and/or searching for other involved abnormal organs must be promptly done. To improve early detection of LCH, general pediatricians should be alerted to be aware of these skin symptoms, and if they persist, a dermatologist, pediatric if available, should be immediately consulted.

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Authors' contribution L. Techasatian contributed to the conception and design of the study, data analysis, interpretation of findings, drafting the article, revising the article, and final approval of the version submitted. S. Poompuen contributed to study conception and data collection. J. Chaiyarit contributed to data processing and data analysis, critical revision of the article, and final approval of the version submitted.

Compliance with ethical standards

Ethical approval and informed consent The study was approved by the institutional review board of Faculty of Medicine, Khon Kaen University, Thailand (IRB no. #HE591399), before enrolling any participants.

Conflict of interest The authors declare that they have no conflict of interest.

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