Dermatology Practical & Conceptual

Infantile Cutaneous Langerhans Cell Histiocytosis Presenting as Benign Skin Lesions: Clinical Pitfalls and Diagnostic Clues

Dimitra Aikaterini Lintzeri[1], Andria Constantinou[1], Annika Vogt[1], Ulrike Blume-Peytavi[1]

1 Department of Dermatology, Venereology and Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Key words: Langerhans cell histiocytosis, Congenital skin lesions, Multisystem

Citation: Lintzeri DA, Constantinou A, Vogt A, Blume-Peytavi U. Infantile Cutaneous Langerhans Cell Histiocytosis Presenting as Benign Skin Lesions: Clinical Pitfalls and Diagnostic Clues. *Dermatol Pract Concept*. 2026;16(1):6064. DOI: https://doi.org/10.5826/dpc.1601a6064

Accepted: June 30, 2025; **Published:** January 2026

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Prof. Ulrike Blume-Peytavi, MD, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, Berlin, Germany; Charitéplatz 1, 10117 Berlin, Germany. ORCID ID: 0000-0003-3528-3752. E-mail: ulrike.blume-peytavi@charite.de

ABSTRACT

Introduction: Langerhans cell histiocytosis (LCH) is a rare but potentially life-threatening hematologic disorder characterized by a wide spectrum of skin manifestations that may mimic a variety of common neonatal and pediatric diseases.

Objectives: To raise awareness of the broad clinical spectrum of cutaneous manifestations important for early recognition.

Methods: Herein, we present seven cases of LCH with diverse skin manifestations, disease type, and course of disease.

Results: Dermatological examination was key in suspecting LCH in all cases, enabling prompt oncological evaluation with skin signs preceding other organ involvement. Skin manifestations ranged from isolated to widespread skin rashes. Common lesions included erythematous, reddish-brown, or skin-colored crusted or scaly papules or maculopapular lesions. However, plaques, patches, vesicles, and urticarial lesions may also occur.

Conclusions: Timely dermatological consultation should be sought in cases of non-resolving, therapy-resistant skin lesions and an unclear diagnosis.

Introduction

Langerhans cell histiocytosis (LCH) is a rare hematologic disorder characterized by an inflammatory neoplasia of CD1a/CD207-positive myeloid precursor cells [1,2]. Its incidence is reported to be 2–9 per million children under 15 years of age per year, with a peak between ages 1 to 3 years and a slight male predominance [1,3,4].

The disease can affect any organ and is currently classified as either single-system or multisystem LCH based on the number of organs involved. It is further categorized as unifocal or multifocal, depending on the number of lesions present in an affected organ. Additionally, LCH is classified as high- or low-risk disease, depending on the involved organs, with high-risk organs including the liver, spleen, and bone marrow [1,4].

The spectrum of cutaneous manifestations in LCH vary significantly, often mimicking various neonatal and pediatric skin diseases, contributing to a high rate of delayed or misdiagnosis [5-7].

Objectives and Methods

In this clinical report, we aim to raise awareness and illustrate the spectrum of clinical manifestations of this rare and potentially life-threatening disease by presenting seven striking clinical cases encountered at our pediatric dermatology outpatient clinic.

Results - Case Presentations

History and Clinical Presentation

Case 1: A six-month-old female presented with progressive skin lesions, initially on her back, spreading onto her trunk two months later. Topical antibiotic treatment prescribed by her pediatrician was ineffective. A preceding urinary tract infection was reported; further history and clinical general examination was uneventful, except for the dermatological assessment, which revealed multiple, reddish, partially crusted papules with diameter 1–3 mm on the trunk (Figures 1a–b).

Case 2: An 11-month-old male presented with persistent lesions on the trunk and extremities of approximately six months' duration that were only partially healing, according to his parents. There was no history of any concomitant disease. The dermatological examination revealed multiple single skin-colored or brownish pinhead-sized papules, partly covered with small crusts at the inguinal area and on the trunk. The scalp had brownish greasy scaling (Figures 1c–d).

Case 3: A three-month-old male presented with persistent skin lesions on his right foot that had been present since birth. The patient was otherwise healthy. Examination showed an erythematous tumor approximately 4 cm in diameter, covered with yellowish crusts on the right heel. Furthermore, confluent erythematous papules and pustules, approximately 0.5–1 cm in size, were seen on the lateral side of the right foot. These lesions were partly hemorrhagic or covered with yellowish-brownish crusts (Figures 1e–f).

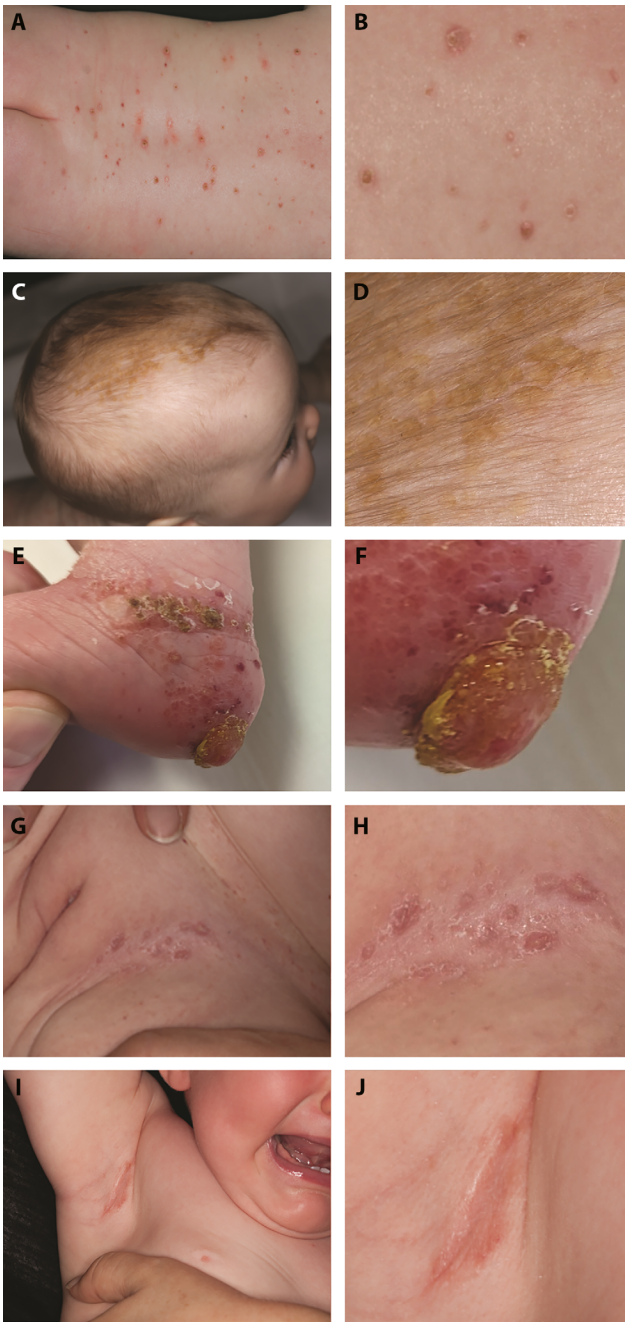

Figure 1. Skin manifestations of Langerhans cell histiocytosis in the presented clinical cases, in panoramic (left) and macroscopic (right) view (Part 1): (a, b) yellow-brownish individual small papules; (c, d) yellow-brownish greasy scales on the scalp confluent in a plaque; (e, f) erythematous tumor covered with yellow crusts on the heel; (g, h) and (i, j) erythematous and yellowish-brownish papules in the flexural areas partly grouped as a plaque.

Case 4: A nine-month-old female presented with recurrent, pruritic skin lesions of three months's duration, spreading from the abdomen to the entire trunk and scalp. Topical

corticosteroids had previously provided only temporary relief. The examination revealed multiple erythematous and yellowish-brownish macules and papules, about 2 mm in size, mainly on the scalp, abdomen, inner thighs, and inguinal area, as well erythematous plaques in the axillary area (Figures 1g–j). Further history and examination proved to be normal. Family history was positive for psoriasis vulgaris.

Case 5: A four-week-old female presented with diffuse skin lesions, severe diarrhea, vomiting, and failure to thrive since the fifth day after birth. The infant's general condition declined. Dermatological examination revealed slightly icteric coloration and multiple diffuse reddish-bluish papules and macules (blueberry muffin rush) (Figures 2a–b).

Case 6: A three-month-old female presented with progressive, persistent skin lesions on her body that had been present since birth. No medical history or family history was reported. The dermatological examination showed disseminated, flat, yellow-brownish papules with a scaly, crusty, or ulcerated surface and a diameter up to 3 mm (Figures 2c–f). In addition, small ulcers were seen in the oral mucosa.

Case 7: A seven-month-old female, referred to the pediatric department of our hospital with suspicion of diphtheria, presented with massive tonsillar hypertrophy with marked whitish coatings and stridor. The patient had a history of recurrent respiratory infections and hospitalization in the pediatric intensive care unit in the previous month due to respiratory insufficiency caused by pneumonia of unknown etiology.

Her parents reported a persistent skin rash since her fourth week of life that had spread from her feet to the entire body. Diagnostic workup in the pediatric clinic revealed an upper mediastinum mass, with suspicion of thymic hyperplasia. Therefore, a thymus biopsy was performed. Our dermatological assessment revealed whitish-yellowish scales and vesicles filled with clear fluid on the scalp and eyebrows. Furthermore, multiple skin-colored or reddish confluent or isolated vesicles and papules were predominant on the patient's back and gluteal and axillary area (Figures 2g–h). A few single vesicles and pronounced redness were seen in the genital area, and papular lesions on both plantae.

Dermatological and Histological Diagnosis

In all clinical cases, the dermatological and histological examinations led to the diagnosis of LCH except for Case 7. In that case, a thymus biopsy was the primary method for diagnosing LCH in conjunction with the dermatological manifestations. In all cases, histological evaluation of the skin biopsy revealed a papillary dermal infiltrate of large cells with light gray cytoplasm and eccentrically located, bean-shaped bent nucleus. The cells stained strongly and homogeneously positive for langerin or CD1a and migrated to the layers of the epidermis (Figure 3). These histological findings are typical of LCH [7,8].

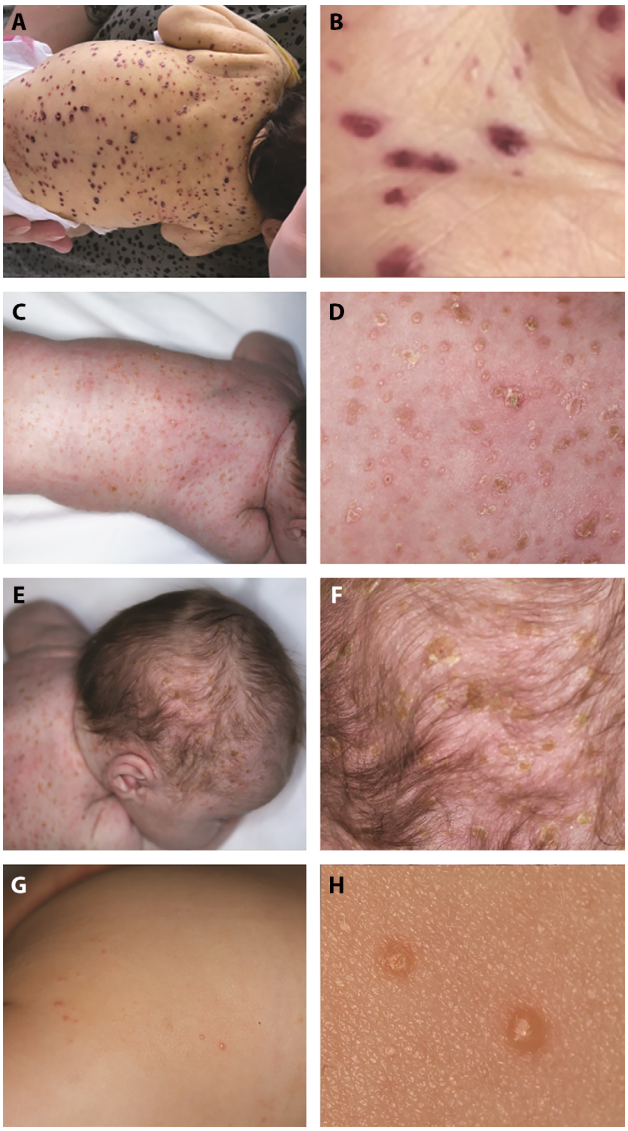

Figure 2. Skin manifestations of Langerhans cell histiocytosis in the presented clinical cases, in panoramic (left) and macroscopic (right) view (Part 2): (a, b) multiple diffuse reddish-bluish papules and macules (blueberry muffin rush); (c, d) yellow-brownish papules with a scaly, crusty, or ulcerated surface on the trunk and (e, f) the scalp; (g, h) firm skin-colored or reddish isolated vesicles and papules.

Course and Outcome

All patients underwent comprehensive evaluation by a pediatric hematologist-oncologist, including total body imaging and hematologic assessment. Three patients (Cases 1–3) were diagnosed with single-system cutaneous LCH and achieved spontaneous remission. Four patients (Cases 4–7) were diagnosed with multisystem LCH: one low-risk case (mandibular and ilium involvement) achieved remission, while the three high-risk cases showed varied outcomes, including excellent response in one patient, long-term remission in another, and one fatal outcome due to therapy-resistant disease. More detailed data on the disease course, management, and outcomes are provided in the Supplementary Material (S1).

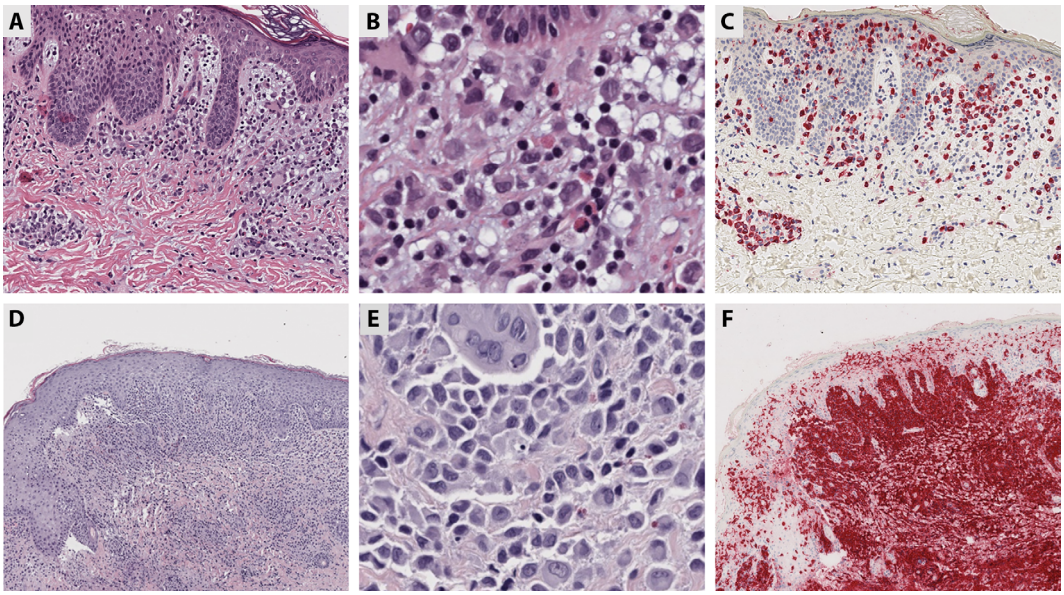

Figure 3. Representative histological findings. The histological findings of Cases 2 (a-c) and 6 (d–f), respectively, show the presence of a cell infiltrate in the papillary dermis consisting of Langerhans cells (magnification b, e). The cells stained strongly and homogeneously positive for langerin (C) and CD1a (f), respectively, and migrated to the layers of the epidermis.

Conclusions

We present seven cases of LCH exhibiting diverse skin manifestations, disease types, and courses. Dermatological examination was instrumental in suspecting LCH as a possible differential diagnosis in all cases, thus enabling prompt pediatric oncological evaluation, with skin manifestations consistently preceding other organ manifestations. This aligns with the existing literature suggesting cutaneous manifestations as the first manifestation in 80% of cases [9]. The skin is the second most affected organ after the bone in LCH patients of all ages (33%) and the most affected organ in patients younger than age 2 years [1,4]. Among patients presenting with cutaneous disease, the majority (87%–93%) have involvement of other organs [10]. Isolated cutaneous disease is less common (2-12%) [11,12].

LCH can present with diverse skin manifestations, ranging from isolated to widespread skin rashes. Common lesions include erythematous, reddish-brown, or skin colored crusted or scaly papules or maculopapular lesions. However, plaques or patches may also occur, which can resemble eczematous or seborrheic dermatitis-like lesions especially when presenting on the scalp [9]. Less common manifestations include vesicles, pustules, urticarial patches hypo- or hyperpigmented macules or maculopapular lesions, purpuric lesions, violaceous papules and plaques, and blueberry muffin spots. Intertriginous areas can develop erythematous, macerated, or ulcerated papules or plaques [1]; lesions are often pruritic [1]. While the trunk, head, and face are most commonly affected [6], the extremities, flexures, intertriginous areas, perianal area, genitalia, and oral mucosa (typically as ulcers) can also be affected.

This wide-ranging spectrum of cutaneous signs in LCH underscores the importance of meticulous clinical observation and skin biopsies to prevent misdiagnosis or delayed diagnosis. A thorough workup of unclear dermatological symptoms is thus crucial. We urge clinicians to examine newborns, infants, and toddlers diligently as this rare but potentially life-threatening disease can mimic many other harmless pediatric skin diseases, thus delaying the diagnosis of LCH. To assist in this process, Tables 1–5 provide a comprehensive list of potential differential diagnoses that should be thoroughly investigated based on the various skin manifestations.

In conclusion, a timely dermatological consultation should be sought in cases of non-resolving, therapy-resistant skin lesions and an unclear diagnosis. This is especially crucial in cases of high-risk, multisystem disease, where prompt initiation of chemotherapy is of vital importance and can result in more favorable disease prognosis and even prevent a fatal outcome.

Acknowledgements: We would like to extend our sincere gratitude to Dr. Tsenka Tomova-Simitchieva, Dr. Davide Neri and Dr. Simone Vogel, who contributed to the care of the patients involved in this case series at the Department of Dermatology, Venereology and Allergology at Charité-Universitätsmedizin Berlin.

Table 1. Differential diagnosis of LCH in newborns and infants with skin-colored, erythematous or brownish papules, papulovesicles or patches with or without crusts.

Skin-colored, erythematous or brownish papules, papulovesicles or patches with or without crusts		
Differential diagnosis	**Distribution**	**Additional findings**
Urticaria pigmentosa	Ubiquitous; primarily on trunk/ extremities; face and palmoplantar involvement uncommon. Mucosal involvement very rare.	Positive Darier's sign
Prurigo/Strophulus infantum	Extremities, trunk, and buttocks; face is rarely involved; no mucosal involvement	Histological findings
Contact dermatitis	Ubiquitous	Contact allergen history; self-resolution after allergen removal
Arthropod reaction	Ubiquitous	Arthropod bite history; linearly arranged lesions, self-resolving within days
Molluscum contagiosum	Especially upper body, upper arm, axillary folds	History of swimming pool visits; localized lesions, positive immunofluorescence
Congenital neoplasms/epithelial tumor syndromes	Ubiquitous	Histological findings

Table 2. Differential diagnosis of LCH in newborns and infants with erythematous scaly or crusted macules, papules or plaques.

Erythematous scaly or crusted macules, papules, or plaques		
Differential diagnosis	**Distribution**	**Additional findings**
Seborrheic dermatitis	Scalp, face, neck and chest region, intertriginous areas	Histological findings
Atopic dermatitis	Onset on face (cheeks), then head, neck, extremities (extensors rather than flexors), possibly involvement of entire body surface. Onset <3 months very rare	Diagnostic criteria for atopic dermatitis are present, histological findings
Psoriasis	Ubiquitous, predilection sites extensors	Histological findings, Auspitz sign, positive family history, etc.
Scabies infection	Ubiquitous, trunk extremities, palmoplantar area; dorsum of fingers and feet, face and scalp	Itching, dermoscopic or histological detection of scabies

Table 3. Differential diagnosis of LCH in newborns and infants with erythematous macerated plaques or macules in the intertriginous areas.

Erythematous macerated plaques or macules in the intertriginous areas		
Differential diagnosis	**Distribution**	**Additional findings**
Candidiasis	Axilla, inguinal region, scrotum or vulva, perianal region.	Positive culture, direct microscopy, and histopathology
Psoriasis inversa	Axilla, inguinal region, scrotum or vulva, perianal region.	Histological findings, family history
Perianal streptococcal dermatitis	Perianal region	Positive smear and/or bacteria culture

Table 4. Differential diagnosis of LCH in newborns and infants with localized or disseminated vesicles or pustules.

Localized or disseminated vesicles or pustules		
Differential diagnosis	**Distribution**	**Additional findings**
Varicella infection	First scalp and oral mucosa, then trunk and extremities	Heubner's star,
		Positive PCR
Herpes simplex virus infection	Local or generalized	Positive PCR, systemic symptoms
Incontinentia pigmenti	Mainly extremities, lateral trunk	Occurring in utero or immediately after birth, phasic disease, high blood and tissue eosinophilia
Bullous diseases (i.e., hereditary epidermolysis bullosa)	Ubiquitous	Mechanically inducible blisters, extracutaneous manifestations, etc.
Infantile Acropustulosis	Predominantly on distal extremities	Recurrent episodes

Table 5. Differential diagnosis of LCH in newborns with a blueberry muffin rash.

Blueberry muffin rash in a newborn		
Differential diagnosis	**Distribution**	**Additional findings**
TORCH-infections	Ubiquitous	Positive history of maternal infection, positive TORCH screen, etc.
Diffuse neonatal hemangiomatosis		Oral, genital, and conjunctival involvement more suggestive
Hematologic dyscrasias		Hematological findings
Vasculitis		Histological findings
Leukemia (e.g. Juvenile myelomonocytic leukemia)		Typical hematological findings
Cutaneous metastases		Primary tumor, histological findings

References

1. Krooks J, Minkov M, Weatherall AG, Langerhans cell histiocytosis in children: History, classification, pathobiology, clinical manifestations, and prognosis. *J Am Acad Dermatol,* 2018. 78(6): p. 1035-1044. DOI: 10.1016/j.jaad.2017.05.059. PMID: 29754885.
2. Rodriguez-Galindo C, Clinical features and treatment of Langerhans cell histiocytosis. *Acta Paediatr*, 2021. 110(11): p. 2892-2902. DOI: 10.1111/apa.16014. PMID: 34192374.
3. Jezierska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M, et al., Langerhans cell histiocytosis in children - a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. *Postepy Dermatol Alergol,* 2018. 35(1): p. 6-17. DOI: 10.5114/pdia.2017.67095. PMID: 29599667.
4. Leung, AKC, Lam JM, Leong KF, Childhood Langerhans cell histiocytosis: a disease with many faces. *World J Pediatr,* 2019. 15(6): p. 536-545. DOI: 10.1007/s12519-019-00304-9. PMID: 31456157.
5. Minkov M, Prosch H, Steiner M, et al., Langerhans cell histiocytosis in neonates. *Pediatr Blood Cancer,* 2005. 45(6): p. 802-7. DOI: 10.1002/pbc.20362. PMID: 15770639.
6. Li Z, Yanqiu L, Yan W, et al., Two case report studies of Langerhans cell histiocytosis with an analysis of 918 patients of Langerhans cell histiocytosis in literatures published in China. *Int J Dermatol,* 2010. 49(10): p. 1169-74. DOI: 10.1111/j.1365-4632.2009.04360.x. PMID: 20883405.
7. Krooks J, Minkov M, Weatherall AG, Langerhans cell histiocytosis in children: Diagnosis, differential diagnosis, treatment, sequelae, and standardized follow-up. *J Am Acad Dermatol,* 2018. 78(6): p. 1047-1056. DOI: 10.1016/j.jaad.2017.05.060. PMID: 29754886.
8. Hussein, MRA, Skin-limited Langerhans' cell histiocytosis in children. *Cancer Invest,* 2009. 27(5): p. 504-11. DOI: 10.1080/07357900802216452. PMID: 19308811.
9. Poompuen S, Chaiyarit J, Techasatian L, Diverse cutaneous manifestation of Langerhans cell histiocytosis: a 10-year retrospective cohort study. *Eur J Pediatr,* 2019. 178(5): p. 771-776. DOI: 10.1007/s00431-019-03356-1. PMID: 30826864.
10. Ehrhardt MJ, Humphrey SR, Kelly ME, Chiu YE, Galbraithet SS, The natural history of skin-limited Langerhans cell histiocytosis: a single-institution experience. *J Pediatr Hematol Oncol,* 2014. 36(8): p. 613-6. DOI: 10.1097/MPH.0000000000000248. PMID: 25171449.
11. Morren MA, Broecke KV, Vangeebergen L, et al., Diverse Cutaneous Presentations of Langerhans Cell Histiocytosis in Children: A Retrospective Cohort Study. *Pediatr Blood Cancer,* 2016. 63(3): p. 486-92. DOI: 10.1002/pbc.25834. PMID: 26586230.
12. Salotti JA, Nanduri V, Pearce MS, Parker L, Lynn R, Windebank KP, Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. *Arch Dis Child,* 2009. 94(5): p. 376-80. DOI: 10.1136/adc.2008.144527. PMID: 19060008.