RMMG
Revista Médica de Minas Gerais

CASE REPORT

Langerhans cell histiocytosis: important differential diagnosis of common childhood dermatoses

Histiocitose de células de langerhans: importante diagnóstico diferencial de dermatoses comuns da infância

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ABSTRACT

Introduction: Langerhans cell histiocytosis (LCH) is characterized by clonal proliferation of immature dendritic cell precursors that infiltrate several organs. The median age of diagnosis in childhood is three years old and can simulate common childhood dermatoses. We present a case report of LCH with initial cutaneous manifestation and subsequent severe multisystemic presentation. **Case report:** Male, one year and seven months old, previously healthy, had erythematous, scaly and itchy lesions in the scalp, eyebrow and cervical region, in addition to inguinal erythema. The patient was treated as seborrheic dermatitis and diaper eczema, without improvement. Subsequently new signs appeared: subungual hyperkeratosis, petechiae in palms and plants, fever, jaundice and otorrhagia. HCL hypothesis was confirmed by histological analysis. Propaedeutic extension showed otorhinolaryngological involvement, affected bones, hematopoietic abnormalities, pulmonary and hepatobiliary involvement. Despite chemotherapy treatment, there was progression to liver failure, infection and death. **Discussion:** The cutaneous manifestations in LCH include pruritic papules, plaques and erythematous nodules on the scalp, diaper area and armpits. They can mimic common early childhood dermatoses such as seborrheic dermatitis, diaper dermatitis, herpetiform dermatitis and scabies, and skin biopsy with immunohistochemistry are essential in cases with progression despite of optimized therapy. **Conclusion:** Isolated skin involvement in LCH generally indicates a better prognosis, however, the possibility of severe systemic involvement justifies rigorous monitoring. Early recognition and treatment are essential for a better prognosis, and should be remembered as a differential diagnosis in childhood dermatoses.

Keywords: Histiocytosis; Langerhans cell histiocytosis; Seborrheic dermatites; Differential diagnosis; Skin conditions; Eczema

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CAAE Ethics Committee:
53203821.0.0000.5149

Opinion Number:
5.137.680

Conflicts of interest:
No.

Recebido em: July 18th, 2023
Aprovado em: November 17th, 2024
Publication Date: May 23th, 2025.

DOI: 10.5935/2238-3182.2025e401-en

RESUMO

Introdução: A histiocitose de células de Langerhans (HCL) é caracterizada pela proliferação clonal de precursores imaturos de células dendríticas com acúmulo em diversos órgãos. A idade mediana de diagnóstico na infância é três anos de idade e pode simular dermatoses comuns da infância. Apresentamos um relato de caso de HCL com manifestação inicial cutânea e posterior apresentação multissistêmica grave. **Relato de caso:** Masculino, um ano e sete meses, previamente hígido, apresentava lesões eritematodescamativas, crostosas e pruriginosas no couro cabeludo, supercílios e região cervical, além de eritema na região inguinal. Tratado como dermatite seborreica e eczema de fraldas, sem melhora. Surgimento posterior de hiperceratose subungueal, petéquias em palmas e plantas, febre, icterícia e otorragia. Hipótese de HCL confirmada por biópsia de lesão do ouvido direito e biópsia cutânea. Extensão propedêutica evidenciou acometimentos otorrinolaringológico, dos sistemas ósseo, hematopoiético, pulmonar e hepatobiliar. Apesar do tratamento quimioterápico, houve progressão para insuficiência hepática, associação com quadro séptico e evolução para óbito. **Discussão:** As manifestações cutâneas na HCL englobam pápulas, placas e nódulos eritematopruriginosos no couro cabeludo, área de fraldas e axilas. Podem mimetizar dermatoses comuns da primeira infância como a dermatite seborreica, dermatite de fraldas, dermatite herpetiforme e escabiose, sendo importante a realização de biópsia cutânea com imuno-histoquímica nos casos com progressão a despeito da terapêutica otimizada. **Conclusão:** O acometimento isolado da pele na HCL, geralmente, aponta um melhor prognóstico, porém a possibilidade de acometimento sistêmico grave justifica um monitoramento rigoroso. O reconhecimento e tratamento precoces são fundamentais para um melhor prognóstico, devendo ser lembrada como diagnóstico diferencial em dermatoses na infância.

Palavras-chave: Histiocitose; Histiocitose de células de Langerhans; Dermatite seborreica; Diagnóstico diferencial; Dermatopatias; Eczema

Introduction

Langerhans Cell Histiocytosis (LCH) is a rare condition caused by the clonal expansion of immature dendritic cells and characterized by the accumulation of pathological histiocytes CD1a+ and CD207+[1]. It occurs mainly in children, with peak incidence between the ages of one and three[2]. There is a wide range of clinical manifestations, depending on the site of infiltration of the neoplastic clones, the skin being frequently affected. Pruritic, erythematous, crusted skin lesions on the face, scalp and skin fold areas may be the first signs of the disease[3] and they simulate common childhood **dermatosis**, causing late diagnosis.

In the event of clinical suspicion, biopsy and immunohistochemistry will confirm the diagnosis. Early specific treatment is essential for better prognosis[1]; therefore, it is important to acknowledge LCH as a possible differential diagnosis in cases of childhood skin lesions. We present a case of LCH with initial cutaneous manifestation, initially treated as extensive seborrheic dermatitis, and subsequent severe multisystem presentation followed by death, despite the establishment of chemotherapy.

Case report

A previously healthy, 1.7-year-old male patient presented pruritic, erythematous, scaly, crusted lesions on the scalp, frontal and cervical regions, in addition to erythema in the inguinal region. The patient was treated with topical medication for seborrheic dermatitis and diaper eczema, but

showed no improvement in subsequent evaluation. There was later appearance of subungual hyperkeratosis, petechiae on palms and soles, fever, jaundice and otorrhagia (Figures 1 to 3). The hypothesis of LCH was confirmed by skin biopsy, which showed proliferation of histiocytic cells in the dermis, with reniform nuclei with slits, eosinophils and intervening lymphocytes, and epidermotropism (Figures 4 and 5). Immunohistochemistry positive for S100 and CD38 and focal cyclin D1.

Figure 1. Erythematous, scaly, crusty, itchy lesions on the scalp.

Figure 2. Erythematous plaque in the intergluteal region.

Figure 3. Erythematous, scaly and crusty lesions on the ear, temple and scalp.

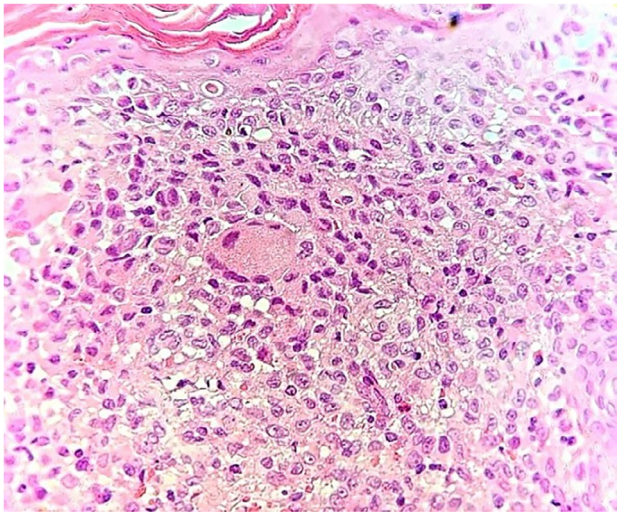

Figure 4. Dermoepidermal junction revealing clonal proliferation of Langerhans cells (elongated, irregular nuclei with inconspicuous nucleoli and pale eosinophilic cytoplasm. HE, 400x). HE, 400x).

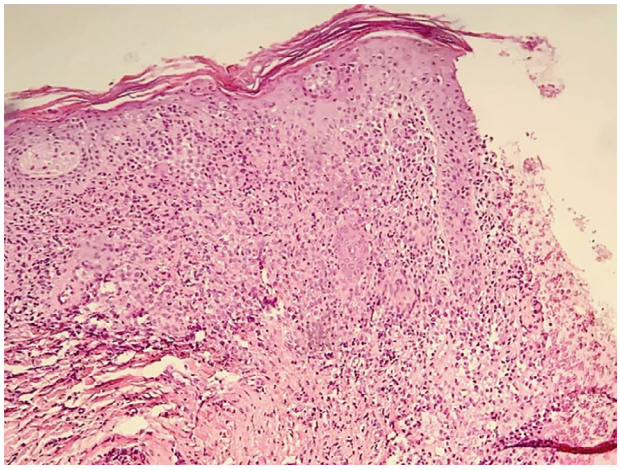

Figure 5. Skin showing dense and diffuse dermal and epidermotropic histiocytic infiltrate with frequent intermingled eosinophils (HE, 100x).

In propaedeutics conducted upon hospitalization, the patient presented normocytic normochromic anemia, reticulocytosis, hypercholesterolemia and hypertriglyceridemia, elevation of canalicular and transaminase enzymes. Abdominal ultrasound showed hepatomegaly, splenomegaly and swollen lymph nodes in the hepatic hilum. Cholangio resonance showed no changes in the bile duct study. Liver biopsy was compatible with secondary sclerosing cholangitis, and right ear lesion biopsy was suggestive of Langerhans cell histiocytosis, with immunohistochemistry marking CD1a, S100, CD68 and Ki67. Magnetic resonance imaging of the skull showed an infiltrative lesion in the right sphenoid bone, with invasion of the homolateral cavernous sinus. Chest computed tomography showed presence of sparse cysts and micronodules in the lung parenchyma. The patient was also submitted to hematological analysis: myelogram showed nonspecific myelodysplastic changes and bone marrow biopsy did not show neoplastic infiltration.

He was started on chemotherapy with vinblastine and prednisolone, in addition to mastoidectomy. To treat the secondary infection, he also received intravenous antibiotic therapy. After clinical stability and the first cycle of chemotherapy, he was discharged for multidisciplinary outpatient follow-up. He was readmitted after a month due to the worsening of ascites and jaundice, and a suspected secondary skin infection. Broad-spectrum antibiotic, and systemic antifungal therapies were introduced, reaching clinical stability. Then, in a pediatric intensive care unit, a second line of chemotherapy with chlorodeoxiadenosine (cladribine) was initiated. Despite all the measures, there was progression of liver failure and a new septic condition, evolving to death.

Discussion

LCH is defined by the accumulation and infiltration of dendritic cells, with characteristics similar to those of Langerhans cells, in different organs of the body[4]. Despite being phenotypically similar to normal Langerhans cells[5], which are dendritic cells of the mucosa and skin[6], pathological LCH cells originate from immature myeloid precursors.

Because it is a rare disease, with a wide spectrum of presentation and multiple differential diagnoses, LCH is a challenging pathology. However, the description of its pathophysiology, treatment and prognosis has had significant advances in recent years.

Although it can occur in any age group, it is predominant in childhood and rarer in adults[2]. The estimated incidence is five cases per million in children under 15, while the median age of diagnosis in childhood is 3 years old[5]. Five to ten percent of patients present lesions since birth or shortly after, but peak incidence occurs between the ages of one and three[2], as occurred in the case reported. Population-based studies have shown higher incidence in Hispanics and lower incidence in black and white/non-Hispanic individuals[7]. As in the concerned case, male patients are predominant. The rate of affection is two male individuals for every three females. Since localized diseases can often spontaneously regress, their prevalence is likely to be underestimated[5].

Regarding its pathophysiology, LCH has been considered for decades a reactive clonal expansion of Langerhans cells; however, in recent years, it has been defined as a neoplasm of myeloid origin, with a significant inflammatory component, which allowed the development of more targeted therapies[6] and increased survival. Somatic mutations are typically found in a proto-oncogene in the MAPKinase pathway (mainly BRAF-V600E)[1]. However, about a quarter of the cases do not present known genomic anomalies. Despite molecular discoveries, LCH is not a classic neoplasm, since there is evidence that its clinical expression is largely caused by the inflammatory properties of the pathological cell clone. In the physiological inflammatory process, foreign antigens stimulate interleukin-1 secretion by Langerhans cells. Interleukin-1, in turn, increases the activity of the MAPK pathway, which can be exacerbated by BRAF mutations, as occurs in LCH[5]. Association with other neoplasms has been reported in rare cases.

The risk factors for its development have not been fully elucidated yet. The patterns of presentation vary from a single lesion or involvement of an isolated organ, which may regress spontaneously, or a disseminated disease, with multiple organ involvement, suggesting a complex pathogenesis. Some studies suggest that neonatal and maternal infections, absence of childhood vaccination, family history of thyroid **diseases**, in vitro fertilization, transfusions during childhood and lower social and economic conditions are associated with a higher incidence of disseminated LCH[6]. Studies that suggest genetic predisposition in some cases, have also shown that the correlation coefficient is higher in monozygotic twins than in dizygotic twins[2].

The distinction between forms of single or multisystem involvement is essential for prognosis and treatment[8], but clinical evaluation associated with histology is not enough for follow-up. Since all organs can be affected, there is the need for a comprehensive evaluation. In the case report in question, multisystem involvement was identified thanks to serial follow-up, associated with extensive propaedeutics with imaging, laboratory and histopathological exams.

Thorough systemic evaluation is essential in all patients in order to identify the extent of the disease and define the specific treatment: comprehensive anamnesis and physical examination, with special attention to the skin, lymph nodes, ears, oral cavity, bones, lungs, thyroid, liver, **central nervous system** and spleen. Growth assessment and a search for specific symptoms, such as polyuria and polydipsia, are also recommended. Recommended laboratory tests include blood count, liver function tests and electrolyte assessment[5]. Recommended imaging tests are long bone, skull and pelvis radiography, as well as liver and spleen ultrasound. Additional propaedeutics should be performed

under specific recommendations[8]. In the case described, in addition to the recommended tests, myelogram and bone marrow biopsy – as recommended in the literature for patients with suspected multisystem disease presenting cytopenia, in order to rule out other causes of **bone marrow failure** – were also performed[8].

LCH is currently classified according to the involvement of single or multiple systems[5]. In multisystem LCH, as presented in this case, two or more organs or systems participate in the diagnosis, with or without involvement of high-risk organs (spleen, liver and/or bone marrow), which occurs in 50% of cases. The mortality rate varies between 10 and 50% for those with multisystem manifestation of the disease, and the prognosis is worse in children under two years of age in case of organ dysfunction[9]. Therefore, the patient in the present report had important indicators of poor prognosis: age group, organ dysfunction and involvement of high-risk organs.

Two-thirds of children present single-system manifestations. The most affected organs are bones (80%), followed by skin (33%), pituitary gland (25%), liver (15%), spleen (15%), hematopoietic system (15%), lungs (15%), lymph nodes (5-10%) and the central nervous system, excluding the pituitary gland (2-4%). General symptoms such as fever, lethargy and weight loss may be present in those cases with single-organ involvement and in multisystem diseases[5].

In patients under two years of age, the most common manifestation is cutaneous, while the skin is the second most frequently involved organ when all age groups are considered[5]. The various presentations include hypochromic or hyperchromic pruritic, macular or maculopapular[4] lesions, papulopustular eruptions similar to chickenpox, erythematous, lichenified or poikiloderma-like plaques, vesicles, vascular tumor-like lesions, macules or purpuric plaques, bleeding ulcers and even yellow-orange papules[5].

The most common sites of involvement are trunk, head, face, limbs, neck, armpits, groin, perineum and buttocks. Other reported areas of involvement include mucous membranes, extremities, flexures, retroauricular regions, perianal, genitalia, sites of previous trauma and eyelids, simulating treatment-resistant chalazion. The oral mucosa may present gingivitis, bleeding, ulceration, pathological fractures of the jaw and loss of teeth. Nail involvement is rare, but may present as onycholysis, paronychia, subungual pustules, hemorrhage or hyperkeratosis and purpuric streaks[5].

The patient described started with cutaneous involvement, the most common in his age group, also in the most common regions. He was diagnosed with a common dermatosis, seborrheic dermatitis, with which it shares clinical characteristics, and was initially treated as such. Corroborating the literature, given the absence of improvement once treatment was initiated, associated with the appearance of new symptoms, LCH was suggested as a diagnostic hypothesis. After the specific LCH treatment was initiated, he showed partial improvement of the lesions, followed by periods of exacerbation and subsequent involvement of the oral and nail cavities.

In 87 to 93% of the cases, skin involvement is associated with multisystem disease, with fever, hepatomegaly, spelanomegaly, bone and pulmonary involvement being the most common associations. Isolated cutaneous disease is observed in only 2% of total cases, and, because of the diversity of presentations, about 16% of patients are not accurately diagnosed with LCH. Common early childhood dermatoses, such as seborrheic dermatitis, diaper dermatitis, dermatitis herpetiformis, scabies, **in addition to HTLV-1 related infectious dermatitis**, can be mimicked by these signs and symptoms. Therefore, it is important to perform immunohistochemistry on skin biopsy in cases where there is progression in spite of optimized therapy[5].

Hepatomegaly, changes in liver function and even jaundice may be present in the context of sclerosing cholangitis induced by histiocytosis. Lymph node involvement occurs mainly in children with multisystem disease[5]. Pulmonary LCH is a rare manifestation that affects mainly adult smokers, but is not part of the disease spectrum in children[2]. Bone involvement in 75% of cases is unifocal, with the skull being the most common site of involvement[5]. However, any bone can be involved, but those of hands and feet are usually spared[6]. Diabetes insipidus – observed in 50% of patients with systemic involvement – is the most common presentation when it comes to pituitary involvement[5].

LCH is diagnosed by the characteristic histology associated with a compatible clinical and/or radiological condition[4]. The anatomopathological study shows eosinophils, neutrophils, lymphocytes and histiocytes in addition to LCH cells, which has been described as eosinophilic granuloma. There may also be necrosis and abscesses. LCH cells are large, oval and mononuclear in appearance, with prominent nuclei and eosinophilic cytoplasms. They stain positively in immunohistochemistry for protein S-100, CD1a and CD207 (langerin), in addition to containing rod-shaped cytoplasmic inclusions: Birbeck granules shown only by electron microscopy[6].

Histological analysis of the concerned patient's skin biopsy showed proliferation of histiocytic cells in the dermis, with permeated eosinophils and lymphocytes, in addition to immunohistochemistry positive for S100 and CD38 and focal cyclin D1. **Despite the unavailability of the CD1a and CD207 markers for skin biopsy, the clinical condition allowed the case to be conducted with a high degree of diagnostic probability.**

Currently, analysis of the *BRAF V600E* mutation in plasma and urine has proved to be a promising tool for diagnosis and monitoring of disease activity[6].

International collaboration through the Histiocyte Society has been seeking to standardize the monitoring and management of these patients. Still, there is debate on the best treatment strategy depending on the extent

of the disease[9]. In children with isolated cutaneous LCH, systemic therapy is recommended for symptomatic or progressive disease only, because it usually resolves spontaneously[8]. Systemic treatment recommendations include cases with involvement of high-risk organs, such as liver, spleen and hematopoietic system and when there is functional involvement of other organs. Multidisciplinary follow-up is recommended[4].

There are several possible drugs for LCH treatment: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, chemotherapeutics, such as vincristine, vinblastine, VP-16 (etoposide), mercaptopurine, methotrexate, cytarabine and cladribine, in addition immunosuppressive or immunomodulatory drugs, such as interferon alfa, anti-TNF-alpha, cyclosporine, thalidomide, among others, such as imatinib, retinoids and bisphosphonates[4]. The difficulties in developing more effective therapies are directly related to the challenges in understanding the pathogenesis of the disease[6].

The targeted therapy is a research area that brings an individualized experimental treatment option: it is targeted at mutations in the MAPK pathway, especially BRAF-V600[8]. Patients with high-risk disease may be ideal candidates for this therapeutic modality, but studies are still in progress.

Relapses or reactivations are frequent in the evolution of LCH. Relapses are defined by a new involvement in a patient whose first involvement was completely resolved. Reactivation, on the other hand, refers to the extension or deterioration of the condition of an already affected organ, as happened with the patient in the case report. Usually, a relapse, in itself, is not fatal, and the prognosis is related to the involvement of each organ, not the number of relapses[4].

Monitoring these patients after treatment is imperative: 88% percent of reactivations occur within the first two years of follow-up. However, it is also important to monitor them also after the two initial years, because some of the sequelae, such as neurodegeneration, may occur several years after the initial diagnosis[8].

It can be associated with several morbidities and permanent consequences, **either due to the course of the disease** or related to its treatment[10]. 71% of the patients with multisystem disease develop sequelae, while only 24% of patients with single-system LCH develop them, the most frequent being diabetes insipidus (24%), orthopedic problems (20%), hearing loss (13%) and neurological sequelae (11%)[8].

The prognostic factors of LCH include extension of the disease at diagnosis, dysfunction of risk organs and initial response to therapy[11]. Isolated skin involvement and limited bone lesions are generally related to a better prognosis and greater chance of spontaneous regression. However, progression to multisystem disease is observed in up to 40% of cases, which justifies a strict monitoring even when only skin lesions are observed[6].

Conclusion

Although rare, Langerhans cell histiocytosis may present high morbidity, and a late diagnosis could be fatal. The polymorphism of its presentations makes it a differential diagnosis for different **diseases**, with involvement of multiple systems, the skin being one of the most affected. Therefore, the reported case emphasizes the importance of clinical suspicion of LCH, both from pediatricians and dermatologists, considering it a differential diagnosis for common childhood dermatoses, especially when resistant to conventional treatments. Its identification, early treatment and multidisciplinary follow-up are fundamental pillars to improve the prognosis of these patients.

Author's Contributions

We describe contributions to the papers using the taxonomy (CRediT):

Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization and Writing – original draft: Daniella Cristina Reis Araújo; Thais Braga Cerqueira; Tatiana Ferreira França; Isabela Boechat Morato. Formal *Analysis, Supervision and Validation*: Romina Aparecida dos Santos Gomes. *Acquisition of Financing and Software*: Not applicable. *Project Management*: Daniella Cristina Reis Araújo; Thais Braga Cerqueira; Tatiana Ferreira França. *Writing – analysis and editing*: Daniella Cristina Reis Araújo; Thais Braga Cerqueira; Tatiana Ferreira França; Isabela Boechat Morato; Romina Aparecida dos Santos Gomes.

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