

Multifocal Cutaneous Langerhans Cell Histiocytosis

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Abstract

Fundaments: Langerhans cell histiocytosis (LCH) is a disease related to the clonal proliferation of myeloid dendritic cells with morphological, immunophenotypic and ultrastructural similarities to Langerhans cells. It is a rare disease, of unknown etiology, common in white males and affecting 1/200,000/year in children under 15 years. This disease present various forms clinics and is very rare the involvement of the skin (less than 10%), mostly with good prognosis and around 30% of the situations can compromise other organs. We report in this article a rare case of cutaneous limited LCH with multifocal involvement and very low response to chemotherapy.

Case report: A six-year-old white girl presenting lesions on the trunk and limbs and progressive increase in number and size, three years ago. In the first dermatological exam was suspected of chronic lichenoid pityriasis, and was prescribed systemic antibiotic therapy, topical corticosteroids and phototherapy, without response. The dermatological examination showed erythematous-violet and infiltrated papules and plaques and residual hypochromic macules in the trunk and limbs. Histopathological examination of the skin revealed dendritic cells similar to LCH (S100⁺, CD1a⁺, CD68⁺). Systemic investigation was normal, confirming cutaneous limited LCH and, despite this, there was low response to Vinblastine and Prednisone therapy.

Discussion: LCH presents an exaggerated clonal proliferation of dendritic cells in different tissues, mainly in bones (80%), skin (33%) and pituitary gland (25%). Therefore, the clinical manifestation changes according to the degree and number of compromised systems and organs and the evolution is unpredictable, ranging from spontaneous resolution to rapid progression and death. In general, skin lesions are the first sign of LCH, manifesting as seborrheic dermatitis-like and refractory dermatitis. The diagnosis is suspected by clinical manifestation and defined by histology and immunochemistry. Therapeutic options should be particularized by the extent and severity of the disease.

Keywords: Histiocytosis; Histiocytes; Langerhans Cell; Classification; Therapy

Abbreviations: LCH: Langerhans Cell Histiocytosis; LCs: Langerhans Cells; NLCH: Non-Langerhans Cell Histiocytosis; MH: Malignant Histiocytosis; CT: Computerized Tomography; CNS: Central Nervous System; SS: Single Site Being; MS: Multiple Sites; MM: Multisystemic Disease

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease of the unknown etiology that is characterized by the clonal proliferation of Langerhans cells (LCs) S-100, CD1a and Birbeck granules or CD207 positive, ie with morphological, immunophenotypic and ultrastructural similarities [1-11].

LCs represent a subtype of antigen-presenting dendritic cells of myeloid origin, with CD1a [7] antigen expressed on the surface and with Birbeck granules in the cytoplasm [3], located in the epidermis and mucosal epithelium of various tissues and organs, comprising a broad spectrum of diseases with different clinical manifestations [1-3,5,6,8-13].

In the past, due to the lack of reliable markers to determine the lineage, clonality or differentiation of proliferative histiocytes, several

clinical syndromes appeared, which led to a lack of definition in the category of histiocytic diseases [11]. As a consequence, Lichtenstein (1953) unified these diseases were under the term 'Histiocytosis X', to cover four subtypes of diseases previously described: Letterer-Siwe, Hand-Schüller-Christian, eosinophilic granuloma and Hashimoto-Pritzker [14]. Subsequently, the Histiocyte Society (1987) suggested the term LCH, based on the definition of Nezelof et al. (1973), local or disseminated proliferative disease of LCs, replacing the term 'Histiocytosis X' and established a reliable mechanism for diagnosis [15,16]. This group described the first classification of this disease which consists of three classes: LCH, non-Langerhans histiocytic cell disease and malignant histiocyte disorders (MH) [15].

Because of this broad clinical spectrum, LCH was stratified according to the degree of tissue and organ involvement and with a variable prognosis depending on the compromise and progression of the disease [5,8,15,17-19]. It was observed that the exclusive involvement of the skin occurs in less than 10% of the cases, mostly with a good prognosis and around 30% of the situations can advance and compromise other systems and organs [5,8,12,20].

This article reports a rare clinical case of cutaneous limited LCH with multifocal involvement and very low response to chemotherapy.

Case Report

A six-year-old child, female, white, with painless and low pruritic lesions on the trunk and limbs, with a progressive increase in number and size, three years ago. It is a previously healthy child with no pathological antecedents. In the clinical suspicion of chronic lichenoid pityriasis, systemic antibiotic therapy, topical corticosteroids and phototherapy were prescribed, but there was no response. Upon physical examination, it presents good neuropsychomotor and respiratory development with absence of visceromegalias, lymphadenopathy, bone deformities or endocrinopathies. Dermatological examination shows erythematous-violet and infiltrated papules and plaques, as well as residual hypochromic macules on the trunk and limbs (Figure 1-3).



Figure 1: Cutaneous Langerhans cell histiocytosis. multiples erythematous-violet and infiltrated papules and plaques on the anterior trunk and upper limbs.

Immunohistochemistry identified LCH-like dendritic cells (S100⁺, CD1a⁺, CD68⁺) (Figure 5) and evaluation by electron microscopy demonstrated the Birbeck granules. In the systemic investigation, laboratory tests, X-rays of the bones and thorax, and CT of the abdomen, skull and thorax were normal. Therefore, despite the extent of the skin involvement, it was confirmed that cutaneous limited LCH. The patient underwent chemotherapy with Vinblastine and Prednisone with partial response, followed by recurrence of the cutaneous lesions requiring replacement by Cladribine.

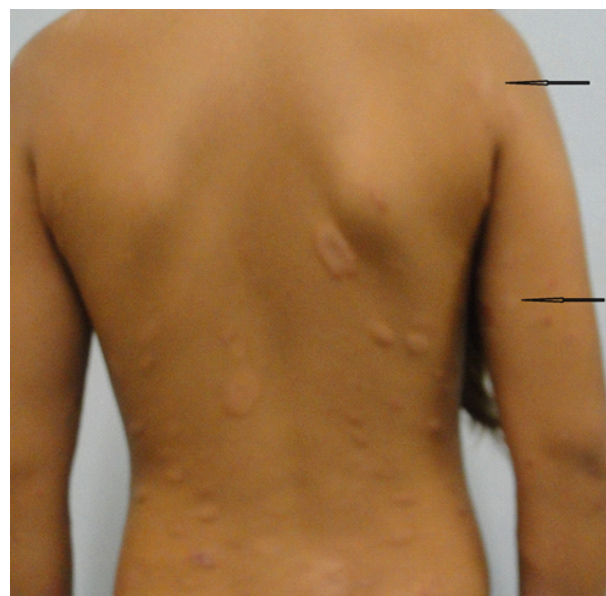


Figure 2: Cutaneous Langerhans cell histiocytosis. multiples erythematous-violet and infiltrated papules and plaques, as well as residual hypochromic macules (dart) on the posterior trunk and upper limbs.



Figure 3: Cutaneous Langerhans cell histiocytosis. multiples erythematous-violet and infiltrated papules and plaques on the lower extremities.

The biopsy of the cutaneous lesion was performed with histopathological analysis that showed polyclonal T cells lymphoid infiltration (CD4⁺ and CD8⁺) and non-granulomatous histiocytes (Figure 4).

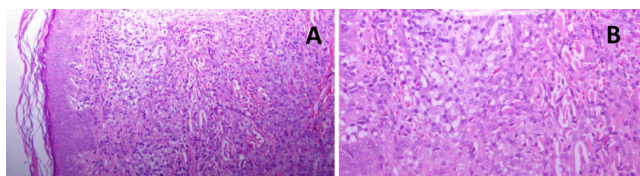


Figure 4: Cutaneous Langerhans cell histiocytosis. Hematoxylin-eosin stained sections of a skin biopsy. A (magnification, X10) show: polyclonal T cells lymphoid infiltration and non-granulomatous histiocytes in dermis and epidermis; B (magnification, X40) demonstrates: infiltrated of oval cells with eosinophilic cytoplasm (Langerhans cells).

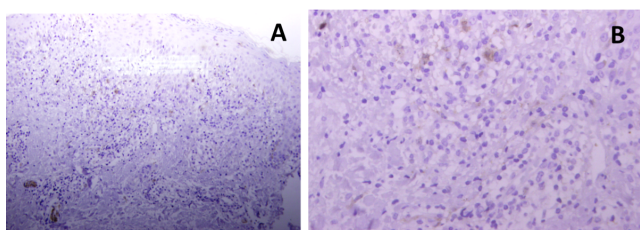


Figure 5: Cutaneous Langerhans cell histiocytosis. The immunohistochemical analyses dermis-epidermis. A (magnification, 10X) and B (magnification, X40), shows: diffuse infiltrated of Langerhans cell Histiocytic-like dendritic cells, positive for S100, CD1a, CD68.

Patient and Methods

The patient in this case report was treated at the pediatric dermatology outpatient clinic and had a confirmed diagnosis of cutaneous limited LCH after investigations with clinical and pathological laboratory and imaging studies of Hospital de Clínicas da Universidade Federal de Uberlândia-MG (HC-UFU), Brazil.

The skin biopsy sample was performed in the small surgery sector of HC-UFU with authorization for application of local anesthetic. Then, the material was sent to the clinical pathology laboratory of the HC-UFU, where the histopathological evaluation was made.

The definitive diagnosis was obtained through the histopathological analysis that identified the presence of dendritic cells, due to the morphological and immunophenotypic characteristics; of S100, CD1a, CD68 by immunohistochemical analysis in paraffin section using monoclonal antibodies; and the Birbeck granules, by electron microscopy.

Discussion

Histiocytoses are rare diseases characterized by the accumulation of macrophages and dendritic or monocyte-derived cells in various tissues and organs in children and adults [2,3]. Langerhans cell histiocytosis (LCH) refers to a proliferative disorder of antigen-presenting dendritic cells, being the most common disorder of the mononuclear phagocytic system, with etiology, pathogenesis and therapy not yet clarified [3,5,8,9].

LCH is a very rare disease (3 to 8/1,000,000 children), more frequent in men (male to female ratio 2:1), affects all age groups, predominantly in children (64%) [1-3,8,9,17-19,21-23]. The skin is the second organ most commonly involved in single-system LCH, with a prevalence ranging from 4.4% to 7.01% of the cases [24].

The clinical presentation of this disease varies according to the disease stage, location and degree of involvement of the organs and systems [2,9]. LCH can compromise only a single site (SS) system and may disappear spontaneously or with multiple sites (MS), and as in multisystemic disease (MM) are often treated with chemotherapy [1,3-5,13,25,26]. Despite the various clinical manifestations, it is common to observe a polarization in the disease spectrum, characterizing three main clinical forms, such as: cases with disease involvement in a single-system with 100% survival with or without therapy; diseases with an intermediate form, of chronic course, involving two or more organs, except hematopoietic, liver and spleen (organs of risk), with high recurrence and severe residual sequelae; and the acute illness, common in infants, disseminated to any organ, causing life-threatening [9]. Therefore, LCH can vary from mild to disseminated forms and from clinical evolution, from spontaneous resolution to rapid progression and death [1,3,5,13]. The main tissues involved are bone (80%), skin (33%) and pituitary gland (25%), liver, spleen, lung and hematopoietic system (15% each), lymph nodes (5% -10%) or CNS (2% -4%, except the pituitary) [3,5,8].

Cutaneous limited LCH is a very rare variant that requires careful investigation to avoid a possible systemic involvement, and presents good resolution and excellent prognosis in cases with few lesions or necrotic lesions or with hypopigmented macules [5,17,24,27,28]. However, its follow-up becomes essential due to the possibility of secondary malignant tumors, such as acute lymphocytic leukemia, lymphomas and histiocytic sarcoma, over time [8,12,17-20,27,29]. While cases of extensive involvement, especially with intertriginous or perineal lesions, require chemotherapy because of the low chances of spontaneous resolution [5].

In general, the most common presentation of cutaneous LCH is a seborrheic dermatitis-like eruption with or without purpuric lesion. Other skin manifestations include: pink or yellowish papules or color of the skin, with or without purples, in addition to scales, erosions, ulcerations, crusts and nodules, are rarely seen pustules or vesicles and can be cured with depigmentation. The sites most commonly involved are scalp and trunk, followed by face, inguinal region, axillary folds, cervical, limbs and lumbosacral [5,7,19,24].

LCH represents a major diagnostic challenge due to the variety of clinical manifestation and similarity with other diseases such as eruptions of seborrheic dermatitis-like and continuous or recurrent diaper dermatitis that does not respond to conventional therapy, which requires an average time of six months from the beginning of the symptoms until its diagnostic definition [3,9]. Diagnosis is based on the association of clinical/radiological findings, histological criteria and immunohistochemical markers for S100 and CD1a, thus discarding the inflammatory, infectious and neoplastic reactions [3,5,9]. The identification of Birbeck granules found in LCs by electron microscopy was initially considered the "gold standard" of the phenotype for the definitive diagnosis of LCH [4,5,13,15]. Currently, they have been replaced by the use of immunohistochemical markers for langerin (CD207), a monoclonal antibody to type II transmembrane protein related to Birbeck granules, as a highly sensitive and relatively specific marker. Then the presence of one or

both markers characterize the LCs phenotype and in association with CD1a⁺ defines the diagnosis of LCH [2-5,9].

The differential diagnosis with LCH is made according to the organ involved, as in forms with: lytic bone lesion with malignant tumors, cervical lymphadenopathy with sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) and cutaneous with seborrheic dermatitis and refractory diaper dermatitis [9,19].

Irreversible sequelae may occur in 30% to 40% of patients due to multisystemic disease involving lesions on the facial bones and base of the skull or treatment, such as changes in height, growth hormone deficiency, diabetes insipidus, partial deafness, cerebellar ataxia, tooth loss, orthopedic problems, pulmonary fibrosis and biliary cirrhosis with portal hypertension [9,19].

Single-system LCH (usually bone, lymph node and skin) presents a benign course with a high chance of spontaneous remission over time [30]. Therefore, the therapies should be particularized by the extent and severity of the disease [5,13,15,30].

Currently, the most indicated therapeutic option for isolated lymph node or nodular cutaneous lesion with exclusion of systemic involvement is surgical excision, or radiotherapy, phototherapy, topical or systemic corticosteroids, meclacetam gel, imiquimod, topical nitrogen mustard [2,5,30]. In cutaneous LCH with MS and with mild forms the response can be obtained in the use of topical corticosteroids and in severe and symptomatic forms can be used the solution of nitrogenized mustard or PUVA with effective response, or also, methotrexate, 6-mercaptopurine/azathioprine, vinblastine, thalidomide and cladribine [2,5,30]. Aggressive treatments should be avoided, since they do not modify the final result [3,5,17].

Regarding the prognosis, the disease with SS involvement has a high survival rate whereas MM disease presents an unpredictable course and a chance of poor prognosis when it compromises a risk organ [9,20].

In conclusion, this article presents a brief review of LCH with an emphasis on cutaneous limited form in young patients, citing a pediatric clinical case with great need for follow-up due to the extent of impairment due to the possibility of developing malignant diseases or systemic involvement (MM).

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