CASE REPORT

Langerhans cells histiocytosis with vulvar involvement and responding to thalidomide therapy - Case report *

Histiocitose de células de Langerhans com acometimento vulvar e com resposta terapêutica à talidomida - Relato de caso

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Resumo: A histiocitose de células de Langerhans é representante de um raro grupo de síndromes histiocitárias, sendo caracterizada pela proliferação das células de Langerhans. Suas manifestações variam de lesão solitária a envolvimento multissistêmico, sendo o acometimento vulvar incomum. Segue-se o relato de caso refratário da doença limitada à pele, em mulher de 57 anos. A paciente apresentava história de pápulas eritematosas ulceradas em couro cabeludo, face, vulva, tronco e axila há seis anos. O diagnóstico da doença é difícil, sendo confirmado neste caso através de estudo imuno-histoquímico e se obteve resposta terapêutica e eficaz, com a administração de talidomida.
Palavras-chave: Histiocitose; Histiocitose de células de Langerhans; Histiócitos

Abstract: Langerhans cell histiocytosis is a member of a group of rare histiocytic syndromes and is characterized for the proliferation of histiocytes called Langerhans'cells. Its manifestations vary from a solitary injury to systemic involvement, and vulvar lesions are uncommon. We describe a refractory case of cutaneous limited disease in a 57-year-old woman. She presented with a 6-year history of an erythematous papular eruption of the scalp, face, vulva, trunk and axillae. The diagnosis is difficult and in this case it was confirmed through immunohistochemical study and clinical improvement was achieved with thalidomide.
Keywords: Histiocytes; Histiocytosis; Histiocytosis, Langerhans-cell

INTRODUCTION

Langerhans cell histiocytosis (LCH) is defined as a clonal proliferation of Langerhans cells in various tissues and its etiopathogeny is unknown. [1,2,3] Its estimated incidence is 1:200.000, and it is rarely seen in adults. [4] Men are more affected than women in a proportion of 2:1 and the disease tends to be more aggressive on the later. [5] The clinical presentation of LCH is variable and practically every tissue can be involved. LCH can be manifested as an isolated lesion in a single organ or as a disseminated disease with organic dysfunction. The systemic disease is more common in infants; 60% to 70% of the cases are diagnosed in patients younger than two years. The LCH restricted to the bones usually develops in children over the age of two , but in 50% of the cases in those under the age of five. The sites most commonly involved are the bones, skin and lymph nodes.[6] Bone involvement is the most commonly observed and develops as osteolytic lesions in flat bones, usually on the skull. [7] Following in frequency are lesions on the lungs and skin, although the primary and exclusive involvement of the skin is not common. [8] Lesions on

Received on 23.12.2010.
Approved by the Advisory Board and accepted for publication on 05.02.2011.
* Work performed at: Hospital das Clínicas da Universidade Federal de Goiás (HC – UFG) – Goiânia (GO), Brasil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

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the genital tract are very rare and the vulva is the site most commonly involved. A recent study identified only 52 cases with genital lesions described on the literature up to its conclusion. [9,10] We report a rare case of LCH in a female patient, adult, presenting with mucocutaneous involvement of various sites including the vulva, without typical bone lesions and with a good response to treatment with thalidomide.

CASE REPORT

White female patient, 60 years old, complained of recurrent erythematous plaques on the labia majora and minora, associated to local stinging sensation, for six years. After two years of the start of the disease lesions similar to secreting nodules developed on the same area and evolved to painful ulcerations, sparse sinequia and cicatricial fibrotic tissue, altering the physiologic vulvar anatomy (Figure 1).

In association with the described lesions the patient also had itchy erythematous-desquamatives papules on the face, close to the hair implantation line and ulcerations on the scalp and temporal area, as well as a glandular enlargement on the left axilla with fibrosis and draining of purulent secretion, similar to hidradenitis (Figure 2). For two years she also had a painless, persistent ulcerated lesion on the oral mucosa, as well as recurrent otalgy and ear discharge.

The laboratory exams were as follow: normal hemogramme, C reactive protein, hepatic and renal functions; non-reagent VDRL, hepatitis B and C, and HIV serology; negative antinuclear factor, rheumatoid factor and e**xtractable nuclear antigen antibodies**; culture from ear secretion swab positive for *Pseudomonas aeruginosa* and from axilla secretion positive for *Staphylococcus aureus*. X-rays from skull, hips, long bones and thorax were normal and head and neck computed tomography showed no alterations.

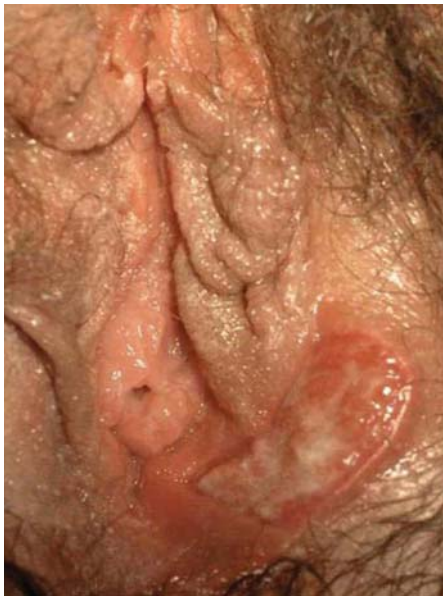

Figure 1: Painful and ulcerated lesions on the labia majora

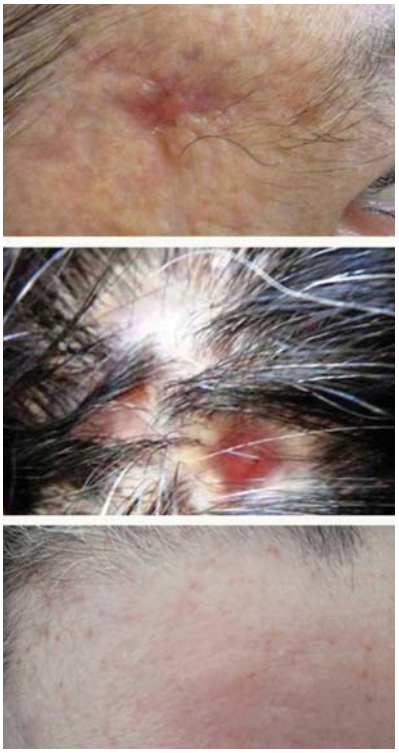

Figure 2: Ulcers on the temple and scalp associated with pruriginous erythematous-desquamative papules close to the hair implantation line

Histopathologic examination form a labia majora fragment revealed epidemis with large areas of ulceration, infiltration of the adjacent dermis by numerous cells (some volumous with abundant eosinophilic cytoplasm and light nucleus and some with reniform aspect and evident nucleoli) permeated by eosinophils and neutrophils and moderate perilesional mononuclear inflammatory infiltrate (Figure 3).

Immunohistochemistry was positive for CD20, CD03 and CD10 in sub-populations of lymphocytes, positive for CD34 in vessels, and proteins S-100, KI-67 and CD1a were positive on the cells tested, confirming the diagnosis of LCH (Figure 4).

Treatment was started with topical dexametasone and 100mg/day of thalidomide, with complete resolution of the cutaneous lesions in four months (Figure 5). When the thalidomide was suspended there was important worsening of the disease and the patient was kept on a maintenance dose of 50mg/day with good tolerance.

DISCUSSION

LCH is also known as a histiocytosis X, term

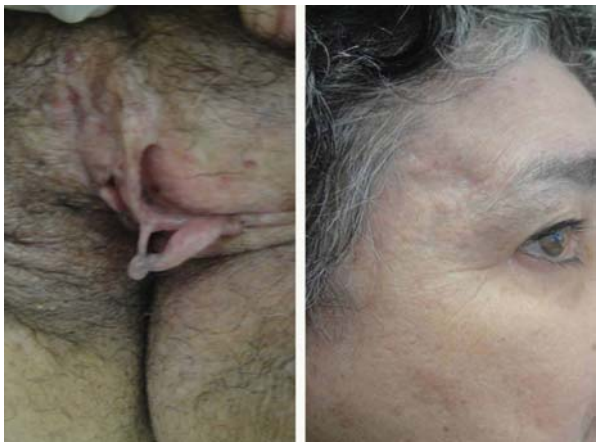

Figure 3: After treatment with thalidomide, with no active lesion but with distortion of the vulvar anatomy and ulceration scar on the temple

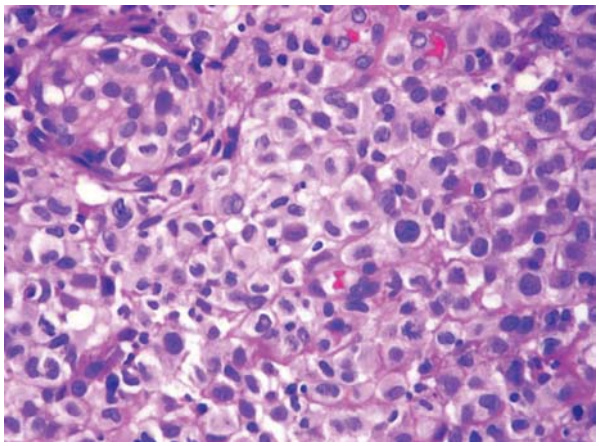

Figure 4: Diffuse infiltrate by the Langerhans cells (large cells with eosinophilic cytoplasm, reniform nucleus and evident nucleoli), permeated by lymphocytes, neutrophils and eosinophils (HE - 400X)

proposed by Lichtenstein in 1953 concentrating the three forms of the disease described by then: **eosinophilic granuloma, the benign accumulation of hystiocytes located primarily on the bones but that also affecting other organs such as skin, lungs and lymph nodes**; Hand-Schüller-Christian disease, chronic and progressive form, presenting with lesions on the skull, exophthalmos and diabetes insipidus, as well as the involvement of other organs; Letterer-Siwe disease, the acute form, disseminated and frequently fatal, with multiple visceral involvement [3] This classification is not being used anymore, it is recommended only the description of the involved sites. [1]

The ethiology is unknown and some believe it is probably a secondary condition to viral infections or immunologic imbalance; neoplasic and genetic origins have also been proposed. [1,4,6,7,9] It can develop at any age but the incidence peak is between 1 and 3 years of age. [2] Patients with focal lesions are usually older than those with multisystem disease. [2] The association of LCH with malignant conditions has been seen in greater frequency. It might be associated with acute leukaemia, myelodisplastic syndrome, Hodgkin disease and solid tumors (adenocarcinoma of the lung, retinoblastoma), and most commonly the diagnosis is concomitant. [9]

The present case is an unusual presentation of LCH in a female patient, with onset in adulthood, with involvement mostly mucocutaneous and without the typical bone lesions. The cutaneous involvement characterizes by papular eruption, usually crusty, ulcerated or hemorrhagic, distributed throughout the seborrheic areas (scalp, ears and upper trunk). Ulcerated plaques are also common in intertriginous areas. [10] Vulvar lesions are usually multiple ulcers, but they can also present as papules, pruriginous rash, nodules or infiltration. [4]

The final diagnosis of LCH includes the clinical aspect and histological and immunohistochemical findings. The disease has similar histological findings in all its clinical forms, characterized by proliferation of Langerhans cells associated with infiltrate of polimorphonuclear cells, eosinophils, neutrophils, hystiocytes and lymphocytes, depending on the duration of the lesion. [3,4] The confirmation of the diagnosis is made through immunohistochemistry, positive for CD1a and S100 protein, as observed in this case, or when cytoplasmic organelles (Birbeck granules) are visualized under electronic microscopy. [1,3,10]

The ideal therapy for LCH has not yet been established, and varies between cytotoxic or immunomodulatory drugs. [9] The clinical variant of the disease and the fact that 10 to 20% of the patients have

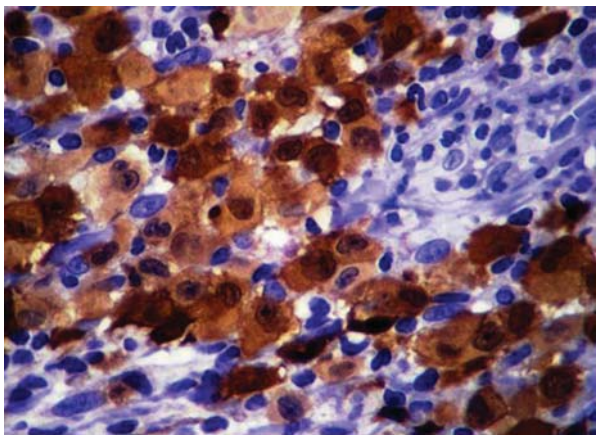

Figure 5: Cytoplasmic positivity to CD1a at immunohistochemistry, characterizing the Langerhans cells

spontaneous regression make it difficult to compare between different therapies and the majority of the available options are based on small case reports. [2,3,4,8,10] Some suggest that the treatment should be conservative and limited to constitutional symptoms or those from affected organs, or based on prognostic facts such as age, extension of the disease, involved organs and complications. [3,5,7]

In case of unifocal disease, like skin or bone lesions, the conduct is expectant or a less aggressive treatment is used, like curettage, topical corticosteroids and nitrogen mustard. [1,7] Local radiotherapy is low doses can be associated with chemotherapy in cases with more extensive bone involvement. [7] Prednisone is the drug of choice in case of lung involvement. [7] Extensive cutaneous lesions can be treated with low dose systemic corticotherapy and chemotherapy (usually a sole drug, most commonly vinblastine, methotrexate and etoposide). [1,7,9]

More recently some studies have shown a good response to thalidomide. [6,11] The drug has antinflammatory and antineoplastic effects and works through inhibition of TNF and IL-6, which have increased expression in LCH. [6,11] Such mechanism of action is supported by reports of improvement of LCH with TNF blockers like etanercept. [6,11] The remission of the disease usually happens within one to three months of treatment and recurrence is common after suspension of the drug. [11] Thalidomide seems to lead to quick healing of the cutaneous and mucosal lesions but it is less effective in extra-cutaneous manifestations. [6] The main side effect of thalidomide is theratogenity, so women in childbearing age should be advised not to fall pregnant during the use of thalidomide (the Brazilian legislation does not allow the prescription of the drug to women of childbearing age that might fall pregnant). [6] Peripheral neuropathy is also a possible side effect, it seems to be dose-dependent and it is not usually seen with treatment of LCH. [6,11] The advantages of thalidomide are the quick effect, easiness of oral use and for a long time, and low cost. [11]

The prognosis of LCH is worse in those under two years of age and the forms with exclusively cutaneous and/or bone lesions tend to have a better outcome. [1,2] Morbidity is related to the structural distortions related to the disease, like pulmonary fibrosis, hepatic cirrhosis, glandular and cognitive dysfunctions. [1,5] Follow-up must be indefinite since the course of the disease after remission is unpredictable, and systemic or malignant disease might develop concomitantly. [7,9]

Despite being rare, fortunately LCH has a benign course on the majority of the cases. However, some patients have a dramatic progression with disturbances on their quality of life, like in the present case. Therefore early diagnosis of the disease with adequate treatment is extremely important in avoiding scarring defects and definitive sequelae. ❑

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How to cite this article/*Como citar este artigo:* Fernandes LB, Guerra JG, Costa MB, Paiva IG, Duran FP, Jacó DN. Langerhans cells histiocytosis with vulvar involvement and responding to thalidomide therapy: case report . An Bras Dermatol. 2011;86 (4 Supl 1):S78-81.