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

INTRODUCTION

Langerhans cell histiocytosis (LCH) is defined as a clonal proliferation of Langerhans cells in various tissues and its etiopathogeny is unknown. Its estimated incidence is 1:200,000, and it is rarely seen in adults. Men are more affected than women in a proportion of 2:1 and the disease tends to be more aggressive on the later. 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. Bone involvement is the most commonly observed and develops as osteolytic lesions in flat bones, usually on the skull. Following in frequency are lesions on the lungs and skin, although the primary and exclusive involvement of the skin is not common. Lesions on...
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. 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 otalgic 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 extractable 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.

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 dexamethasone 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
proposed by Lichtenstein in 1953 concentrating the three forms of the disease described by then: eosinophilic granuloma, the benign accumulation of histiocytes 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. This classification is not being used anymore, it is recommended only the description of the involved sites.

The etiology is unknown and some believe it is probably a secondary condition to viral infections or immunologic imbalance; neoplastic and genetic origins have also been proposed. It can develop at any age but the incidence peak is between 1 and 3 years of age. Patients with focal lesions are usually older than those with multisystem disease. 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.

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. Vulvar lesions are usually multiple ulcers, but they can also present as papules, pruriginous rash, nodules or infiltration. 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 polymorphonuclear cells, eosinophils, neutrophils, histiocytes and lymphocytes, depending on the duration of the lesion. 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.

The ideal therapy for LCH has not yet been established, and varies between cytotoxic or immunomodulatory drugs. The clinical variant of the disease and the fact that 10 to 20% of the patients have
spontaneous regression make it difficult to compare
between different therapies and the majority of the
available options are based on small case reports.3,5,6
Some suggest that the treatment should be conser-
"ative 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 corticos-
steroids and nitrogen mustard.4,7 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).4,7,9

More recently some studies have shown a good
response to thalidomide.4,11 The drug has antinflam-
atory 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 suspen-
sion of the drug.6 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 cuta-
"neous and/or bone lesions tend to have a better out-
come.1,2 Morbidity is related to the structural distort-
tions related to the disease, like pulmonary fibrosis,
hepatic cirrhosis, glandular and cognitive dysfunc-
tions.1,5 Follow-up must be indefinite since the course
of the disease after remission is unpredictable, and
systemic or malignant disease might develop concomi-
tantly.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 dis-
turbances on their quality of life, like in the present
case. Therefore early diagnosis of the disease with ade-
quate treatment is extremely important in avoiding
scarring defects and definitive sequelae.

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