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Journal of Cosmetology

Letterer-Siwe Disease and the Use of Thalidomide for the Treatment

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Case Report

Volume 2 Issue 1

Received Date: July 24, 2018

Published Date: August 24, 2018

Abstract

Langerhans cell histiocytosis is a proliferative, reactive disease, characterized by clonal accumulation of abnormal dendritic cells of bone marrow origin. This work describes a case of a four-month old African-American boy showing clinical, histological, immunohistochemical and electron microscopy evidence for the diagnosis of the Letterer-Siwe disease. He was treated with betamethasone and thalidomide, with relatively good control of the disease but, after the corticoid was withdrawn, clinical symptoms were aggravated, suggesting the patient should be transferred to the local pediatric oncology service, for chemotherapic treatment.

Keywords: Histiocytosis; Langerhans-Cell; Letterer-Siwe Disease; Betamethasone; Thalidomide

Introduction

Langerhans cell histiocytosis (LCH) is a proliferative, reactive disease, characterized by the clonal accumulation of abnormal dendritic cells of bone marrow origin [1]. Proliferation of Langerhans cells, lymphocytes, macrophages and eosinophyls is observed, which may extend to nearly all organs [2]. The dendritic cells express the positive immunophenotype for CD1 and/or contain cytoplasmic Birbeck granules under electron microscopy. The presence of markers such as S100, CD207 (Langerin), CD68 and the factor XIII A are useful in the differential diagnosis of other histiocytoses [3].

According to the Histiocyte Society, histiocytoses may be divided in three groups: those affecting dendritic cells, macrophage-related diseases and malignant histiocytic disorders. The criteria for the diagnosis of LCH include

clinical features, as well as anatomopathological and immunohistochemical results. The presumptive diagnosis may be based upon clinical pathological correlations, but a definitive diagnosis requires the demonstration of positive staining for S100 and CD1a in lesional cells, and the sine quá non identification of Birbeck granules under electron microscopy (gold standard) or CD207 positivity [4].

Individuals of all ages can be affected, although there seems to be a greater incidence in children between 1 and 4 years of age. Congenital manifestations, as well as the description of the disease in an 84 years-old patient, have been reported. The frequency with which LCH affects men doubles compared with that observed in women [1,3,5].

This work describes the case of a boy showing clinical, histological, immunohistochemical and electron microscopy evidence for the diagnosis of the Letterer-Siwe disease.

Case Report

We present a four-month old African-American boy showing whitish lesions in the cervical and frontal regions since birth. From the age of one and a half month on, erythemato-papulose lesions covering all body surfaces were also observed. Further examination evidenced erythematous, vesiculous, crostose lesions, which showed to be friable in the cervical and axillary regions, as well as in the anterior and posterior thorax, abdomen, gluteus and in the inguinal region, all permeated by hypochromic areas. The skin also showed to be friable, with an enanthema being observed in the oral mucosa. Desquamation with transudation was seen in the scalp, but it was discrete over other body surfaces. Palm hands showed erythemato-purpuric lesions (Figure 1). Weight loss, decrease in diuresis and a continuous irritable crying were reported. The mother denied any problems during pregnancy or delivery (42 weeks and 5 days). There was no consanguinity between parents.

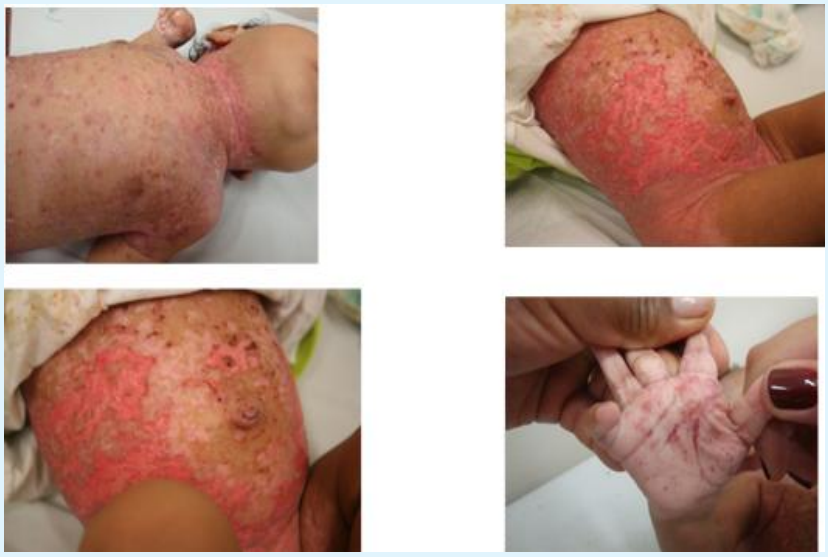

Figure 1: Pre-treatment erythematous, vesiculous, crostose lesions, which showed to be friable in the cervical and axillary regions, as well as in the anterior and posterior thorax, abdomen, gluteus and in the inguinal region, all permeated by hypochromic areas. Plam hands showed erythemato-purpuric lesions.

The histopathological exam revealed an intense dermal edema with infiltration of histiocitary cells, CD1a and S100 positivity, as well as the presence of Birbeck granules under electron microscopy (Figure 2). Laboratory tests showed anemia, discrete lymphocytosis and monocytosis, and a decrease in the platelets count. Hepatic and renal functions were normal. The bone inventory was within the normality standards, showing no lytic lesions.

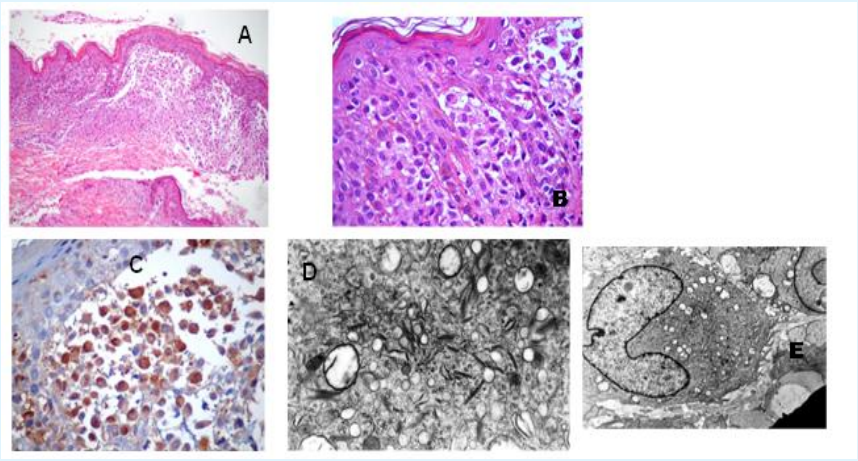

Figure 2: Letterer Siwe disease. Aand B: a dense and diffuse infiltrate of langerhans cells beneath the epiderm (H&E); the cells stain strongly with CD1a (C), and have several Birbeck cytoplasmic granules on transmission electron microscopy (D). Original magnification X40 (A); x400 (B,C); x1600 (inset); x8000 (E).

With the diagnosis of the Letterer-Siwe disease, 2 mg/day of betamethasone were prescribed, improving significantly the cutaneous symptoms, although the boy still showed the easy crying and the opisthotonus position. For this reason, thalidomide was concomitantly introduced in the dosage of 25 mg/day, which resulted in an improvement of these symptoms in a one-week period (Figure 3). Corticoid withdrawal was then initiated, maintaining thalidomide use. This procedure, however, aggravated the symptoms once more, for which he was transferred to the reference pediatric oncology service, for chemotherapy.

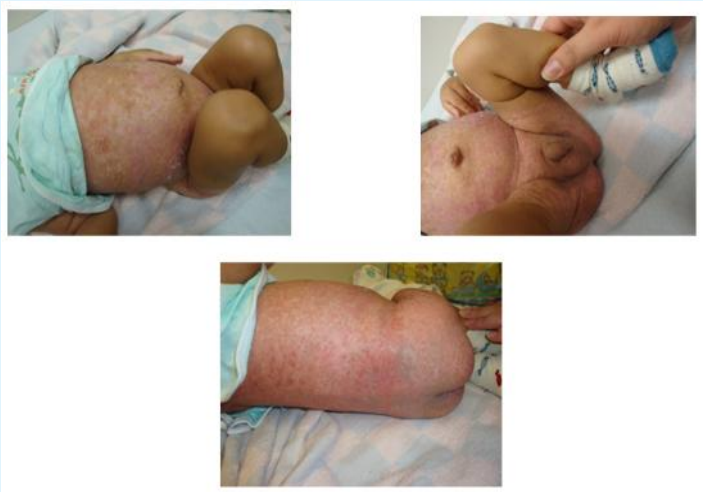

Figure 3: After 2 weeks of treatment with betamethasone and thalidomide.

Discussion

Epidermal Langerhans cells are originated in the bone marrow. Similarly, histiocytes are derived from progenitor lineages of neutrophils and macrophages of the marrow. Progenitor cells differentiate in mature monocytes in the blood stream, under the regulation of colony stimulating factors. Monocytes in the peripheral

blood migrate to several tissues and differentiate in macrophages. Tissue macrophages are called histiocytes. These cells are highly plastic, and may differentiate depending on the stimulation of different cytokines, such as beta-interferons, interleukin-1, tumor necrosis factor-alpha, and the granulocyte-macrophage colony-stimulating factor [6].

Langerhans cells histiocytosis is a poorly known pathogeny. There are hypothesis on whether it would have a neoplasic or inflammatory origin, and discussions on the existence of some immunological, genetic or infectious (mainly viral) triggering factor [7].

Symptoms are especially detected during infancy, with more than 50% of cases being diagnosed between ages 1 and 15. The incidence in individuals under 15 years-old is of 4.5 in one million [1,7].

Clinically, the Letterer-Siwe disease develops within the first two years of life, in an acute and disseminated manner. Cutaneous lesions are extensive and classically similar to those of seborrheic dermatitis, affecting the scalp, face, thorax and perineum. It may also be observed as papules, pustules, vesicles, and petechial or purpuric lesions. Systemic signals and symptoms may include fever, anemia, lymphadenopathy, osteolytic lesions and hepatosplenomegaly [1,3,4,6,7].

When evaluating a patient suspected to bear LCH, a complete laboratory investigation must be carried out: complete hemogram, coagulogram, hepatic function and urinary osmolarity. It is also recommended to make a radiologic evaluation of both the skeleton and lungs. If any alterations in these exams are observed, the investigation must be broadened: tomography, magnetic resonance, pulmonary function, and hepatic and pulmonary biopsy [4].

Treatment depends on the number of organs affected. Skin-limited, exclusive manifestations do not need treatment, with topic corticotherapy being suggested. Localized bone lesions may be curetted, an enough procedure for both diagnosis and treatment. Also, the infiltration of intralesional corticoid or radiotherapy in low dosages may be indicated. For systemic symptoms (with multiple affected organs), treatment is controversial, since both corticoids in high doses or chemotherapy using a drug alone or in combination, have been suggested [4].

McClain et al carried out a stage II study prescribing thalidomide for patients showing LCH symptoms [2]. It was demonstrated that thalidomide may be effective in localized disorders affecting skin or bones through the inhibition of TNF excess. However, in patients showing more advanced and extensive symptoms, this drug efficiency could not be demonstrated.

The disease prognosis depends on the involvement of risk organs, like bone marrow, liver, spleen, and the response to the therapy. Another important factor is if the disease is a single-system disease or a multisystem disease. In the first case, the recurrence rate in 5 year is 20%, with favorable prognosis and low rate of sequelae. On the other hand, multisystem disease has a potential risk of mortality, with higher risk of recurrence (about 50%) and sequelae [8].

In the reported case, after clinical, laboratorial and initial histopathological investigations, we chose as a dermatological service to treat the patient with betamethasone in a relatively high dose (2 mg/day), which was weekly evaluated. Since the patient showed an intense pruritus and irritability, 25 mg/day of thalidomide was associated with the treatment, with good clinical and laboratorial responses (improvements on monocytosis and on the platelets count). However, when the corticoid was withdrawn, clinical symptoms were aggravated, suggesting the patient should be transferred to the local pediatric oncology service, for chemotherapic treatment.

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