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CASE REPORT

Early diagnosis of Langerhans cells histiocytosis: case report

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Abstract

Langerhans' cells histiocytosis is a disease that belongs to the group of histiocytic disorders and is considered a rare pathology. It results from a proliferation and accumulation of cells of the phagocytic mononuclear system, including Langerhans' cells. This paper reports a case of a 4-year-old patient who presented a growing, swollen, nodular, depressible and mobile lesion in the right retroauricular region, without pain or phlogistic signs for 6 months, besides erosive and necrotic lesions in the first and second right molars. The confirmatory diagnosis was made by biopsy and immunohistochemistry. This is a study of the medical record, histological evaluations, laboratory and imaging tests of the patient, with the aim of discussing the pathology, making the diagnosis and treatment earlier.

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a disease in the group of histiocytic disorders and is considered a rare pathology¹. Its first description occurred in the mid-1900s, when a pathology called Hand-Schuller-Christian Disease was reported, which is described as an eosinophilic granulomatosis².

Even today, there is no consensus regarding the pathogenesis of LCH. There is ambivalence around whether it is an inflammatory or neoplastic disorder. The most defended idea is that it would be a neoplastic pathology due to the fact that patients present mutations in the BRAF proto-oncogene (serine/threonine-specific protein kinase), as mutations in this location are related to the development of different types of cancer².

Regarding epidemiology, it is estimated that around three to five cases occur per million inhabitants per year, mainly between the 1st and 3rd decades of life³. It is understood that it is a more common disease in pediatric patients⁴, affecting approximately one to two cases per million live births in newborns⁵.

Clinical manifestations are varied and can affect different organs and systems, with a great variability of signs and symptoms. Therefore, for practical purposes, a system was created in which the patients are classified in two ways: single-organ LCH, in one or multiple foci; and multisystem LCH, which affects multiple organs, including bone, gastrointestinal system, lung, bone marrow, eyes, skin, lymph nodes, and central nervous system (CNS). Furthermore, the organs involved can be divided into high risk, such as liver, spleen and bone marrow; or low risk, such as skin, bone, lung, lymph nodes and pituitary gland in the CNS. It is worth mentioning that 80% of LCH cases present with bone lesions⁶.

The definitive diagnosis of LCH requires, through biopsy of the lesions, an immunohistochemical reactivity to CD1a, CD207+ (Langerin) and/or S1005 markers. Furthermore, in electron microscopy it is possible to find Birbeck granules (microscopic structure found inside the cytoplasm of Langerhans cells)⁷. Other laboratory and/or radiological tests can be used to define the extent of the disease, but are not used as a diagnostic criterion, such as positron emission computed tomography (PET-CT) with fluorodeoxyglucose (FDG), which is used especially to locate bone lesions⁸.

The prognosis is closely related to the involvement of high-risk organs⁹. However, it also depends on other factors, such as age at diagnosis, initial response to treatment, site of involvement and location of the mutation in the BRAF gene⁹.

The present study presents a case of Langerhans cell histiocytosis in a pediatric patient with facial involvement and a literature review on the subject. The objective was

to discuss this pathology, making diagnosis and treatment increasingly earlier.

CASE REPORT

Four-year-old, Caucasian, male patient, with uneventful, full-term pregnancy and cesarean section, at 41 weeks, and with adequate neuropsychomotor development. It presented a growing, swollen, nodular, depressible and mobile lesion in the right retroauricular region that began six months ago, without the presence of signs of inflammation, in addition to erosive lesions and areas of necrosis in the first and second molars on the right (Figure 1). The x-ray of the face showed no changes and the ultrasound of the right retroauricular region showed the absence of cortical bone measuring 20 mm in length, with an increase in retroauricular soft tissues. Tomographic study demonstrated a lytic lesion with a soft tissue component, affecting the right posterior parietal bone, measuring approximately 31 x 11 x 33 mm, in contact with the corresponding lambdoid and squamous sutures. Extraction of the affected teeth and biopsy of the adjacent tissue were performed, which showed proliferation of histiocytic cells positive for S10 protein. To date, no genetic screening has been carried out to investigate possible mutations in the BRAF gene.

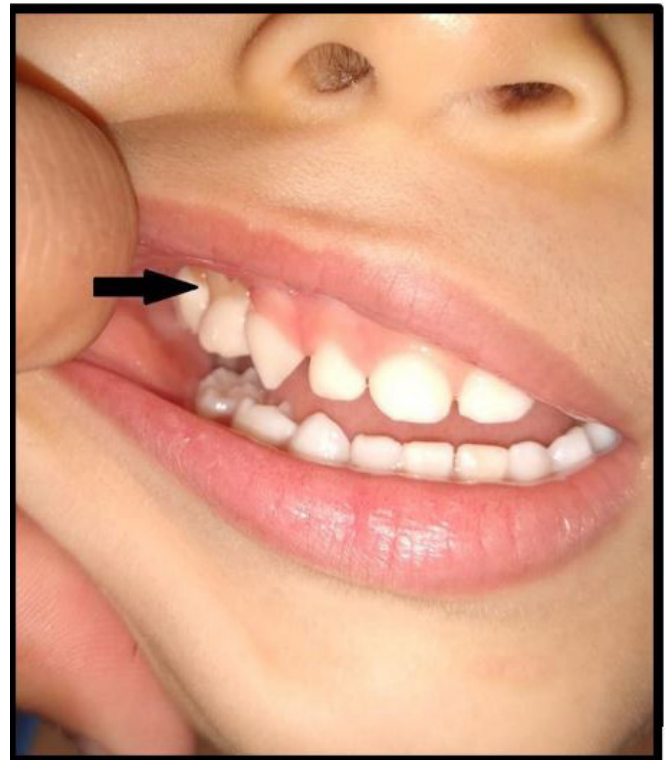


Figure 1. Patient's dental arch showing erosive lesions and necrosis in the first and second molars on the right.

He was referred to a reference oncology hospital where positron emission computed tomography (PET-CT) was performed in March 2021/ which demonstrated glycolytic metabolism of the lytic lesion with soft tissue involvement, located in the right parieto-occipital region of the skull, with SUVmax of 5.4 (there is a greater consumption of glucose in this area when compared to the other regions captured by the exam, being indicative of malignant tumors). Treatment was started with weekly intravenous vinblastine 6mg/m², associated with oral prednisone 40 mg/m² daily. A new PET-CT scan was performed two months later, which demonstrated a good response to treatment, starting to use intravenous vinblastine 6 mg/m² every three weeks and oral prednisone 40 mg/m² for five days following treatment with vinblastine. He presented an adverse reaction after the first chemotherapy session (CT) with a dry cough, using diphenhydramine hydrochloride and hydrocortisone in the days preceding CT, without the need for a change in the chemotherapy regimen. He also used prophylactic sulfamethoxazole + trimethoprim and ondansetron in case of nausea or vomiting.

It is worth mentioning that follow-up was carried out with new PET-CT scans. As previously mentioned, there was a change in the SUVmax value from 5.4 in March/2021 to 4.1 in May/2021, with a decrease in glycolytic metabolism, which indicated a good response to treatment. Furthermore, 6 months later, when a new PET-CT was performed, there was an absence of significant glycolytic metabolism in the lytic lesion, which could indicate complete regression of the initial lesion.

Therefore, in this patient it is possible to state that there was a good evolution with complete regression of the lesions after the 8-month course of treatment. It will continue to be monitored for another 1 year in case of possible recurrence, with an estimated 52 weeks of treatment.

COMMENTS

Langerhans cell histiocytosis is a rare disease¹ with a pathogenesis that has not been completely elucidated^{2,10}. It is characterized by intense and abnormal proliferation of dendritic cells, originating from the bone marrow, with characteristics similar to Langerhans cells². Currently, it is understood that these cells are more similar to immature dendritic cells of myeloid origin than to Langerhans cells themselves².

Regarding the etiology, there is still divergence in the literature about the origin of LCH, with no consensus on whether it is a disease of inflammatory or neoplastic origin¹⁰. The inflammatory origin is based on the abundant infiltrate of T cells and inflammatory cytokines, found in the sites affected by the disease⁷. However, neoplastic origin is defended as the most accepted idea today, due to

the clonal capacity of the cells present in the lesions and the discovery of mutations in the BRAF oncogene, most commonly, the BRAF V600E mutation, in addition to the good response to chemotherapy⁷.

Epidemiologically, LCH is mostly a pediatric disease⁴, with a predilection for males¹¹ and an average diagnosis of 3 years of age¹². Regarding ethnicity, the patient is similar to the majority, as 80% of cases are from the Caucasian population³.

A challenge encountered is estimating concrete data regarding HCL cases in Brazil, since the disease-specific ICD (D76.0) is not found in the epidemiological system of the IT department of the Brazilian Public Health Care System (DATASUS) of the Ministry of Health of Brazil. In addition to this fact impacting the underdiagnosis of the disease, it also makes it difficult to implement new public policies, understanding the need for investment in new therapies and new scientific studies related to this pathology. This brings more relevance to the case presented, serving as a means of disseminating knowledge about the pathology and its main characteristics.

The disease has several clinical manifestations and can affect bones, skin, mucous membranes and/or internal organs⁶. In the case described, there were reports of lytic lesions in 02 foci: skull and maxilla, being the most common form of presentation as it is bone involvement, occurring in around 80% of cases⁶. In this case, it is classified as low risk because it does not involve so-called high-risk organs, such as the liver, spleen and bone marrow^{12,13}.

The confirmatory diagnosis of LCH is made through biopsy of the lesion with histological analysis of the tissue, which must show immunohistochemical reactivity for the markers CD1a, CD207 + and/or S100⁷. In the case in question, diagnostic confirmation was made through the proliferation of histiocytic cells positive for S100 and CD1a protein, in a biopsy performed on the right posterior maxilla. Additionally, other complementary tests are necessary to rule out other diagnostic hypotheses and evaluate organic function in systemic LCH, such as blood count, plasma protein levels, hepatogram, inflammatory proteins, thyroid hormones and urine type 1^{6,7}. The patient in question only had a restricted bone lesion, with no changes in routine laboratory tests. In relation to imaging exams, PET-CT plays a fundamental role in the staging and monitoring of lesions⁸, having been performed on the patient at the time of diagnosis and during therapeutic intervals, confirming the regression of the disease.

The postauricular location of the patient's lesion dictated the course of treatment used, as due to its proximity to the central nervous system, more aggressive approaches are necessary¹², and first-line treatment with vinblastine and prednisone was chosen¹⁴. It is worth mentioning that, even though the patient in question has shown therapeutic success, for most patients this response

is uncertain, since the most common mutation is BRAF V600E⁴, which is related to a more aggressive disease and resistance to first line treatment agents¹⁵. In these cases, it is necessary to use second-line agents, which have a higher degree of toxicity and are related to greater long-term side effects in ¼ of patients¹⁵.

The prognosis of LCH varies according to the presentation of the disease, age at diagnosis, response time to treatment and degree of disease dissemination¹³. The patient had a better prognosis, firstly, due to the fact that there was no involvement of target organs and had a satisfactory response to treatment in the first six weeks, with a high degree of disease regression. Along with this factor, the pathology was limited to the maxillary and retroauricular region and the age at which symptoms began was after 2 years of age, which corroborated a more favorable prognosis.

It is important to highlight that, having been monitored by a trained multidisciplinary team, the patient reached the diagnosis in just 6 months from the onset of the first symptom. This data is different from the usual reality, as complaints normally tend to be non-specific, causing patients to spend years treating and researching different differential diagnoses depending on the symptoms they present, such as seborrheic dermatitis (presence of non-specific scaling), mastoiditis (edema and retroauricular redness) and leukemia (lymph node enlargement and ecchymosis).

A worldwide obstacle concerns first-line treatment with vinblastine and prednisone. This is because in several studies the most frequent mutation of the disease (BRAF V600E) can be seen, which characterizes a more resistant presentation and a higher rate of relapses when treated with this therapy. Furthermore, second-line treatments, which would be preferred in these cases, have high rates of toxicity and long-term adverse effects. Therefore, it is necessary to create therapeutic approaches that are more appropriate to the most common genetic profile, aiming to guarantee the best prognosis and lower recurrence in these patients.

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