

Case Report Article

Different oral manifestations of langerhans cell's histiocytosis: report of two cases

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Abstract

Introduction: Langerhans Cell Histiocytosis (LCH) is a disorder characterized by abnormal proliferation of CD1a+/S-100/CD207+ Langerhans cells. It has a peak of incidence between one and three-year-old, with a prevalence in males than females. It may affect several anatomical locations. **Objective:** to report two cases of oral manifestations of HCL, which exemplify the broad age range affected by the disease and its different clinical presentations. **Material and methods:** This is a retrospective, descriptive, observational study in the format of a technical note, represented by two clinical cases that demonstrates the different Oral Manifestations of Langerhans Cell's Histiocytosis. **Case report:** a 47-year-old man presenting ulcerated lesions in hard palate and gingival region and a three-year-old boy with a diffuse swelling at the posterior mandible were diagnosed with HCL at the same institution. **Conclusion:** the HCL can manifest itself as a single lesion or as a multisystemic and potentially fatal disease. The clinician should be attentive to diagnose it at an early stage, to avoid worse complications and sequelae to the patient.

Introduction

Langerhans Cell Histiocytosis (LCH) is a disorder characterized by abnormal proliferation of CD1a+/S-100/CD207+ Langerhans cells [9]. LCH has a peak of incidence between 1 and 3-year-old [8], with a prevalence in males than females [3].

It may affect several anatomical locations, such as bones, skin, liver, lung and hematopoietic and neuroendocrine systems [7], and may manifest itself as a single lesion or as a multisystemic and potentially fatal disease [6]. The bone is affected most frequently, and jaws are involved in 10% to 20% of patients [7].

The diagnosis of oral LCH lesions is generally challenging, mainly because it has a very varied clinical presentation [7], including gingival recesses, periodontal pockets and teeth mobility, simulating periodontal disorders, or simulating malignant neoplasms such as Ewing's Sarcoma, Lymphoma, Fibrosarcoma and Giant Cell Granuloma. The most common radiographic findings are osteolytic lesions with irregular edges and sclerotic margins [6].

Because it is an aggressive disease with potential to involve several organs and because of such varied clinical and radiographic characteristics, the clinician should be attentive to diagnose the LCH at an early stage, to avoid worse complications and sequelae to the patient.

The objective of this study is to report two cases of oral manifestations of HCL, which exemplify the broad age range affected by the disease and its different clinical presentations, reaffirming that it is a challenging diagnosis for the clinician.

Material and methods

This is a retrospective, descriptive, observational study in the format of a technical note, represented by two clinical cases that demonstrates the different Oral Manifestations of Langerhans Cell's Histiocytosis. Epidemiological data, medical history, and photographic records were obtained from the medical records, after parental and patient consent, following the precepts for publication without identification of the patients. In order to complement the paper, current literature searches were made using the MeSH Database through the keywords: Histiocytosis; Langerhans-Cell; Jaw Neoplasms; Mandible; Pediatrics. Based on the results found, a brief discussion on the subject was made.

Case report

Case 1

A 47-year-old male patient referred to Erasto Gaertner Hospital, Curitiba, Brazil (HEG), with a left iliac bone tumor associated with painful symptoms, in 2015. A CT scan of the pelvis revealed a destructive mass in the left iliac and retroperitoneal and iliac lymph nodes on the left, measuring up to 12 mm. Resection of the lesion was performed by the Orthopedic Department and the results of the anatomopathological and immunohistochemical examination confirmed the diagnosis of Langerhans Cell Histiocytosis (LCH) through the positivity of S100, Vimentin, CD1a, CD68 and Ki67 cells. The treatment proposed by the Clinical Oncology Department was six cycles of chemotherapy every 21 days with Cyclophosphamide 750 m/m², Vincristine 4 mg, Etoposide 100 mg/m² and Prednisone 100 mg.

About 5 years after the initial diagnosis, the patient was referred to the Oral and Maxillofacial Surgery Department of the same institution for evaluation of oral lesions. Intra-oral examination revealed an ulcerated lesion measuring approximately 0.7 cm in left hard palate, with sensitivity to palpation and an evolution of approximately 1 month. The patient also presented an ulcerated lesion with the same clinical characteristics, but with a shorter evolution time and measuring approximately 0.3 cm in the gingival region, at the premolar area (figure 1). The patient presented good oral hygiene, teeth in good condition and denied comorbidities or history of smoking.

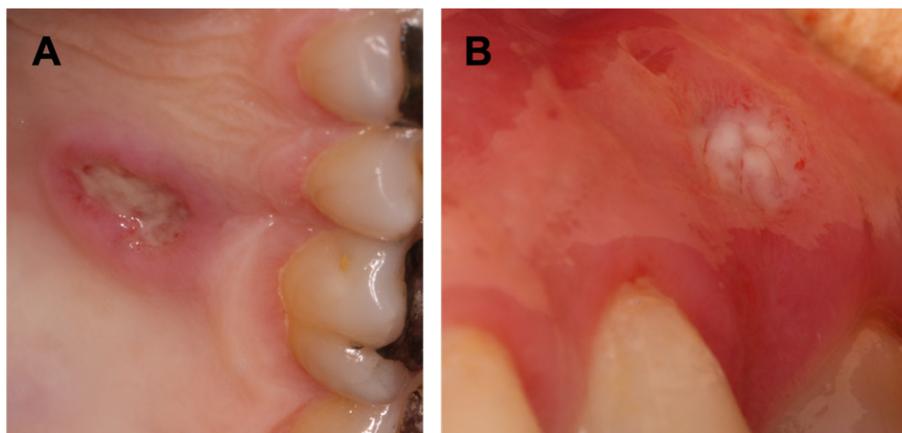


Figure 1 - Initial aspect of the intraoral ulcerated lesions. A) Hard palate lesion; B) Gingival lesion

An incisional biopsy under local anesthesia of both lesions was performed. The anatomopathological examination of the collected materials revealed fragments of hyperplastic mucosa with cellular infiltration of inflammatory characteristics. Immunohistochemical analysis confirmed the diagnosis of Langerhans Cell Histiocytosis, through the positivity of CD1a, S-100 and Ki67 cells (table I). The postoperative panoramic X-ray of the patient showed no bone involvement. In a follow-up visit one month after the biopsy, the patient presented total regression of the gingival lesion and decrease in the size

of the hard palate lesion (figure 2). He reported only a discreet discomfort associated with the lesion, denying significant dysphagia or another symptomatology.

Table I - Immunohistochemical Markers

Antibody	Result
Ki67	Positive in 20% of neoplastic cell nuclei
CD1a	Positive
S-100	Positive
CD68	Negative

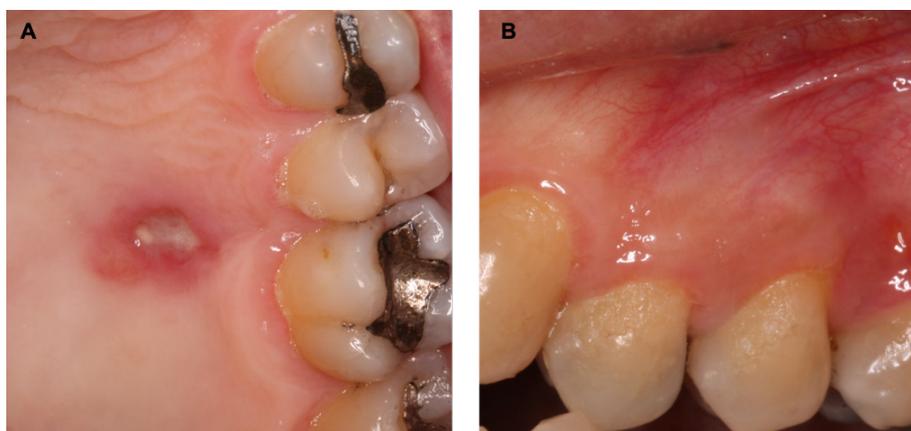


Figure 2 - The aspect of the ulcerated lesions after 1 month, showing improvement. A) Hard palate lesion; B) Gingival lesion

The patient was again referred to the medical team to define conduct. Since the injuries were asymptomatic, the doctors chose to follow up the injuries, without starting treatment. The patient continues under the care of the Orthopedic, Clinical Oncology and Oral and Maxillofacial Surgery teams of HEG.

Case 2

Male patient, three years old, was referred to the Pediatric Department of Erasto Gaertner Hospital, Curitiba, Brazil (HEG), for evaluation of persistent swelling in right submandibular region that appeared within the past 20 days, initially treated as parotiditis and after as odontogenic infection, with no improvement nor aggravation. The responsible reported that the patient complained of pain only during palpation and did not present fever or weight loss. As a medical history, the patient

had iron deficiency anemia, currently off-treatment, without further diseases nor medications in use.

At initial physical exam, was observed a diffuse flaccid swelling occupying the entire extension of the right mandibular ramus, with normal skin, from the angle to the pre-auricular region and a palpable lymph node in the right submandibular region, of approximately one cm, non-fixed and flaccid (figure 3). Primary dentition was complete, all teeth in good condition, without cavities, fillings, lesions or fistula.

A CT scan was performed and showed an osteolytic lesion measuring 34x10x19mm, causing erosion of the internal and external cortices of the mandible with extension to soft tissues, displacing the masseter muscle (figure 4). A periosteal reaction was also observed on both bone faces, suggesting an aggressive lesion. Edema of the adipose tissue and thickening of the deep fascia was observed. It was also identified three enlarged lymph nodes,

with up to 18 mm, on the IB and IIA cervical levels, near the right facial vessels. Pharynx, oral and nasal cavities, parotid and submandibular glands, larynx and thyroid gland all normal. The range of signals indicated aggressiveness.

An incisional biopsy of the lesion was performed under general anesthesia. Anatomopathological result was of a fusocellular neoplasia with discrete nuclear anaplasia, without mitosis or necrosis. The immunohistochemical analysis was consistent with polygonal/fusiform cell proliferation, with giant cell permeation, suggesting a Central Giant Cell Lesion (table I).

Although Central Giant Cell Lesion was a suitable diagnose, was not the major one and the histology was not definitive. Also, the team felt the need to be completely sure about the nature of the lesion, to rule out any chance of a malignant disease. So, the patient underwent a new biopsy under general anesthesia. A new sample was collected from the same spot as previous and through the same intraoral access performed before (figure 5). The largest cervical lymph node was also removed by the pediatric surgeon and also some of the affected soft tissue nearby. The anatomopathological analysis of this new pieces revealed atypical proliferation of histiocytes and eosinophils associated with extensive fibrogenic activity, bone neof ormation and osteoclast giant cells. The lymph node analyzed showed multifocal involvement by atypical and eosinophilic histiocyte aggregates. The immunohistochemical diagnosis confirmed the diagnosis of Langerhans' cell histiocytosis through positivity for CD1a, CD68, S-100 and Vimentin (table II).



Figure 3 - Facial initial aspect of the patient. On this photo, one may see a discrete diffuse from the angle to the preauricular region, with normal covering skin

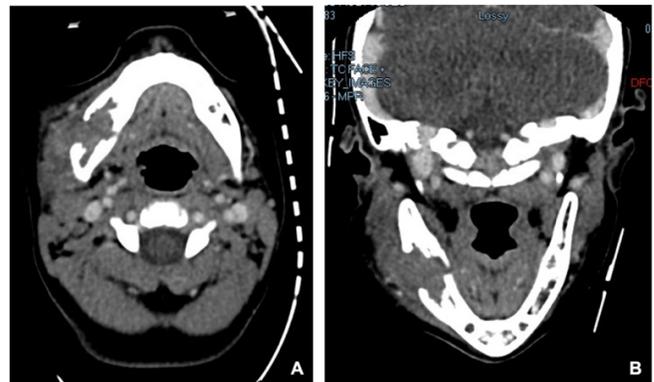


Figure 4 - Computed tomography of the neck showing the initial aspect of the lesion, with erosion of the internal and external cortices of the mandible and extension to soft tissues. A) Axial section; B) Coronal section



Figure 5 - Intraoperative image showing the aspect of the pathological cavity during biopsy

Table II - Immunohistochemical Markers

Antibody	Result
Vimentin	Positive
CD1a	Positive
S-100	Positive
CD68	Positive

The patient was then referred for treatment with the Pediatric Oncology team, and the proposed treatment was a combination of Vimblastine 6 mg/m² for 6 weeks and Prednisone 40 mg for 4 weeks.

After one month of treatment, a new CT showed a reduction in the dimensions of the lesion and there was no more evidence of mass involving soft tissues. No more lymph nodes were identified at IB and IIA levels. Currently, the patient remains in follow-up, without the use of medication. Last CT showed nearly complete resolution of the mandible lesion and absence of altered cervical lymph nodes.

Discussion

Langerhans Cell Histiocytosis (LCH), previously known as Histiocytosis X, is a disorder characterized by abnormal proliferation of CD1a+/S-100/CD207+ Langerhans cells [9]. The Histiocytosis X nomenclature was recommended by Lichenstein in 1953 to embrace three clinical varieties with similar histological characteristics: eosinophilic granuloma, Lettere-Siwe disease, and Hand-Schuller-Christian disease. The term “histiocytosis” refers to the proliferation of histiocytes and other inflammatory cells, where the letter “x” denotes the unknown etiology of the disease. In 1973, the term HCL was adopted because the histiocytes involved have a phenotype similar to the Langerhans cells found in normal skin and mucosa [5].

LCH has a peak of incidence between 1 and 3-year-old [8], with a prevalence in males than females [3]. In the second presented case, the patient has an age compatible with that described in the literature, while the patient in case one was diagnosed as an adult, over 40 years of age.

Depending on the site of accumulation and proliferation of these cells, LCH may be classified into three different categories: unifocal or multifocal, that affects only a single organ (typically bone or skin) and multisystemic form, that may cause organ dysfunction when affects high risk organs such as lung, liver or bone marrow [6]. In our cases, the first patient presented multisystemic HCL, evolving bone, oral mucosa and lymph nodes, while the second patient presented the multifocal form, with bone lesion and lymph node involvement.

The bone is affected most frequently, and bony lesions occur most commonly in the skull, ribs, vertebrae and mandible. Jaws are involved in 10% to 20% of patients. The most frequently intraoral site is the posterior mandible [7], and according to the literature, oral lesions may be the first or only sign of manifestation of LCH [6]. Not corroborating with the literature, our patient in case number one presented oral manifestation of the disease about five years after the initial diagnosis in the pelvis region.

The diagnosis of oral LCH lesions is generally challenging, mainly because it has a very varied clinical presentation, and its characteristics may simulate infectious or periodontal diseases. Gingival lesions may cause bleeding and gingival retraction, commonly associated with loss of dental insertion and mobility [6]. When mucosa is involved, it is characterized by irregular surface lesions, with or without involvement of adjacent bone [9]. LCH lesions in the jaws usually cause swelling, pathological

fracture and severe dental mobility. The most common radiographic findings are osteolytic lesions with irregular edges and sclerotic margins [6]. The cases presented in our study confirm this great variability of HCL clinical presentations. The adult patient presented ulcerated lesions in the mucosa, without involvement of gnathic bones, while the pediatric patient developed a mass in the posterior jaw region, without involvement of oral mucosa.

As signs and symptoms, both of our patients presented swelling accompanied by discomfort and pain symptoms related to bone lesions (mandible or pelvic region), which according to the literature, are the most common signs and symptoms of bone HCL [1].

The differential diagnosis of LCH with bone involvement includes malignant neoplasms, such as Ewing's Sarcoma, Lymphoma, Fibrosarcoma and aggressive benign lesions like Giant Central Cell Granuloma [6]. Anatomopathological and immunohistochemical exams must be combined to define the diagnosis of LCH.

The microscopic examination of the diseased tissue shows cells such as eosinophils, neutrophils, lymphocytes and histiocytes, in addition to Langerhans cells. This set of cells is traditionally described as Eosinophilic Granuloma. Abscess and tissue necrosis may also be present. During the analysis, it is evident the intense proliferation of histiocytes and positivity of CD1a, CD207 and S100 cells. In addition, Langerhans cells have an important pathognomonic sign, the so-called “Birbeck Granules”. In both of our cases, CD1a cells were positive during immunohistochemical analysis [2].

The prognosis of the lesion depends on the involvement of risky organs, such as liver and bone marrow, and also depends on the patient's response to initial therapy. According to recent literature, there is no defined protocol for the treatment of HCL due to its rarity and variability in relation to location and severity. Cases of multifocal or multisystemic HCL often require systemic treatments, such as chemotherapy. Children with multisystemic HCL are usually treated with cytotoxic drugs and corticosteroids, alone or in combination. Also, unifocal cases of the disease, which have not responded well to surgical treatment, may be indicated for Chemotherapy or Radiotherapy [4]. In case number one, the surgical resection was not chosen at first because the removed lymph node was compromised by the disease, which represented a multifocal disease. If the tumor was restricted to the primary site – the mandible –, the treatment of

choice would have been surgical resection. In case number two, the patient underwent by surgery and chemotherapy, but currently he is just monitoring the diseases, due the oral lesions are asymptomatic.

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