



Oral manifestations of Langerhans cell histiocytosis (LHC): Review of scientific literature and case report

Manifestaciones orales de la histiocitosis de células de Langerhans (HCL): Revisión de literatura y reporte de un caso

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a dendritic cell disease. It is classified into two variations: localized or disseminated. Frequency per year is 1 in 200,000 children under 15 years of age. Aggressive forms of the disease are mainly found in younger children. This disease presents oral manifestations, which can sometimes be the first expression of the condition. With relative frequency, jaws can result affected. Radiographic study of the condition shows well circumscribed, osteolytic lesions imparting a pathognomonic «floating teeth» image. Patients can be afflicted with lymphadenopathy, fever, irritability, anorexia, pallor, middle ear otitis and anemia. The present article conducts a literature review and presents the case of an 11 month old male infant. This case presents histiocytosis oral expressions, incidence, clinical characteristics, diagnosis and treatment.

RESUMEN

La histiocitosis de células de Langerhans (HCL) es una enfermedad de las células dendríticas. Se clasifica en formas localizadas o diseminadas. La frecuencia por año es de 1 en 200,000 niños menores de 15 años de edad. Las formas agresivas ocurren sobre todo en niños pequeños. La enfermedad cursa con manifestaciones orales, pudiendo ser éstas, la primera manifestación de la enfermedad. Los maxilares pueden ser afectados con relativa frecuencia. En el estudio radiográfico se observan lesiones osteolíticas con bordes bien definidos dando una imagen de «dientes flotantes», lo cual es el signo patognomónico. Pueden aparecer linfadenopatías, fiebre, irritabilidad, anorexia, palidez, otitis media y anemia. Se realiza una revisión de literatura y además se presenta el caso de un lactante varón de once meses de edad, con el propósito de dar a conocer las manifestaciones orales por las que cursa la histiocitosis, su incidencia, características clínicas, diagnóstico y tratamiento.

Key words: Langerhans cell histiocytosis, cervical lymphadenopathy, floating teeth, premature exfoliation.

Palabras clave: Histiocitosis de células de Langerhans, linfadenopatías cervicales, dientes flotantes, exfoliación prematura.

INTRODUCTION

Histiocytosis is the general term used to indicate some reticulo-endothelial system diseases. These conditions are the product of accumulation or primary proliferation of the mononuclear phagocytic system (MPS). Histiocytosis encompasses two types of immune cells:

- 1) Macrophages
- 2) Dendritic cells¹

HISTIOCYTOSIS CLASSIFICATION

Histiocytosis, according to Histiocyte Society², is traditionally classified into three main groups:

Class I: (Langerhans cell histiocytosis), formerly called X histiocytosis

Class II: Histiocytosis of other mononuclear phagocytes different from Langerhans cells

Class III: Histiocytic malignancies.^{1,3,4}

Nevertheless, Langerhans cell Histiocytosis is the currently preferred term. It is classified into localized or disseminated form.

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1. Localized form. Skin or self-involution expression, bone affection only, (eosinophilic granuloma) normally found in long bones.⁵
2. Disseminated form: Normally found in infants or children under 3 years of age, presenting a generally compromised physical condition. In these cases, the following characteristics are frequently found: lytic bone lesions compromising neighboring soft tissue areas, lung damage as well as repeated infections. This form has predilection for seboreic areas (scalp and skinfolds).²

Recently, a new classification has been proposed according to the producing cell: Langerhans cell histiocytosis is now part of the dendritic cells diseases group.^{1,2}

LCH three «traditional» forms are:

- Eosinophilic granuloma: It encompasses only patients with isolated or multiple⁴ bone lesions, lacking other expressions of the disease.^{1,6} It is a lytic lesion more frequently found in the skull, lower jaw, femur or vertebrated bodies. It bears good diagnosis.^{1,7}
- Hand-Shuller-Christian disease: A disseminated, chronic variation of this condition. It consists of multiple bone lesions associated to diabetes insipidus as well as exophthalmus (through retro-orbital granuloma). Many patients can also present lymphadenopathy, dermatitis, splenomegaly or hepatomegaly.^{1,4} Lesions found in the mouth are the following: ulcers, edema, hyperplasia and gingival necrosis, lesions of the maxillary bones and tooth loss, taste disorders, halitosis, protracted wound healing. It affects children between 3 and 6 years of age. It bears positive diagnosis.
- Letterer-Siwe disease. This is an acute and disseminated form of the disease, common in children under two years of age. It is characterized by fever, rash, lymphadenopathy, hepatomegaly and splenomegaly, osteolytic lesions, general skin eruption (petechiae, scaly papules, nodules and vesicles). From a stomatological point of view, the following traits can be found: ecchymosis, ulcers, gingivitis, periodontitis, bone disease and tooth loss. It bears severe prognosis.^{1,6,7}

BACKGROUND

LANGERHANS CELL HISTIOCYTOSIS (LCH)

Encompasses disorders traditionally called X histiocytosis.⁸ This is a general name allotted to a group of

syndromes which encompass any abnormal increase in the number of certain immune cells called histiocytes.⁹ These cells include monocytes, dendritic cells and macrophages. It is a rare condition characterized by the accumulation of Langerhans dendritic cells in granulomatous lesions more frequently located in bone and skin, but which can also be found in many other organs.¹

PATHOLOGICAL ETIOLOGY

LCH etiology is as yet unknown. Recent research has established which particular cell generates this disease. Ultra-structural and immune-histo-chemical similarities have been found between the proliferative cell of this disease and Langerhans cell, found normally in epidermis and mucosa.⁴

PATHOLOGICAL ANATOMY

The specific pathological finding is the presence of a dendritic cell (DC) within the components of the lesion.¹

Microscopically, the lesion appears as a yellowish granuloma. Cells similar to normal LC cells can be observed. These are mononuclear cells, 15 to 25 µm in diameter, with moderate cytoplasm, pale eosinophil, a centered or somewhat off-center nucleus, kidney shape, with a nuclear membrane cleft or fold appearing as a «coffee bean»,¹⁰ sometimes erythrophagocytosis can equally be found¹¹ (*Figure 1*).

When observed under electron microscope, Birbeck granules^{1,8,12,13} or «racket» bodies can be observed.¹⁰

INCIDENCE

The National Pediatric Institute (Instituto Nacional de Pediatría) reports a total 224 patients treated in the period 1970 - 1999. Out of this number, gingival lesions were identified in 21 patients; 16 of these patients presented dental lesions.¹⁴

Frequency found for this disease is 1 in 200,000 children under 15 years of age.^{1,10} It can appear at any age. Incidence peak is found to be between 1 and 3 years of age. Patient mean age is from 5 to 6 years. A predilection for males has been observed. Aggressive forms occur mainly in young children.¹

CLINICAL PICTURE

Clinical picture depends on the disease and compromised tissue or organ.¹² It appears in varied forms, since any organ or system can be compromised. Nev-

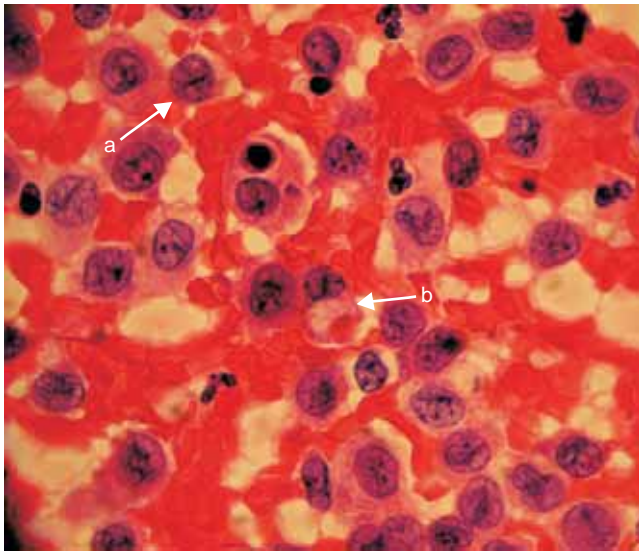


Figure 1. Left inguinal lymphatic ganglion imprint showing «coffee bean» appearance (a) as well as erythrophagocytosis (b) harvested from present case patient. Sample dyed with Hematoxylin and Eosin.

ertheless, there are preferential locations.¹ In disseminated disease instances, many organs are compromised, and several general expressions of the disease can be present, such as fever, anorexia, weight loss, anemia, hemorrhagic manifestations (petechiae on the trunk) asthenia and irritability.¹²

Bone lesions: Bone lesions are present in most patients with localized disease form and are very frequent in patients afflicted with the disseminated disease variation.¹² Single bone eosinophilic granuloma is the most frequent and benign clinical expression. Hematopoietic active bones are involved, mainly those pertaining to the skull, followed by femur, lower jaw, pelvis and vertebrae.

According to their location they give rise to typical clinical pictures of varied degree.¹ It is common to find lytic bone lesions with involvement of neighboring soft tissue, which give rise to a geographical skull; in skull base bones they give rise to exophthalmos and diabetes insipidus; in mastoids to exudation and otorrhea, in vertebrae to vertebral crush. In cases where lysis occurs in the jaw, there will be a «floating teeth» radiographic image.^{1,4,7,8,12,15,16}

Lesions in the mouth: In nearly half the cases there are lesions in gums and teeth.³ The disease normally initiates in the periapical region of the tooth. The posterior area of the lower jaw is the most affected

zone,^{8,16} causing erosion of the lamina dura. This erosion can elicit a mandibular ramus height decrease.⁸

There is pain and gum inflammation (swelling). Upon palpation, a tumefaction is found, which corresponds to Langerhans cell accumulation. This elicits oral ulceration with the possibility of tooth loss.¹⁶

Radiographically, teeth are observed as «floating teeth».^{1,3,6,8,11,16} A typical lesion presents lytic shape, as well as well circumscribed borders since, especially in the early stages of the disease, they are surrounded by a radiolucid^{1,8,16} granulomatous material which displaces forming teeth buds.^{1,16}

Oral lesions can be the first and only expression of the disease; This is the case in 35% of all cases.¹⁶ It has been reported that 30% of LCH cases with oral or perioral compromise, present cervical lymphadenopathies.^{6,8}

Premature loss of deciduous teeth associated with bone loss is a clear sign of histiocytosis. Anterior teeth involvement is infrequent, and indicative of a negative prognosis.¹⁶

In some cases, there is loss of deciduous teeth with precocious replacement and early eruption of permanent teeth. This is frequently the consequence of prepubescent periodontal disease associated to *Actinobacillus actinomycetencomitans* and is conducive to tooth mobility and loss when the patient is about three years old.⁸

Skin lesions: Skin lesions are observed in over one third of children afflicted with LCH. They can be the first and sometimes only symptom as is the case in oral lesions. Typical lesions appear diffuse, papular and exfoliative, similar to seborrheic dermatitis lesions. They are located in the scalp, folds, and perineal region.

Lymph nodes and thymus: The cervical region is the most frequent location.

Liver: In cases of disseminated disease hepatomegaly is frequent.¹

Spleen: In cases of disseminated disease splenomegaly is present in 5% of cases.

Lung: 40 to 50% of the children afflicted with disseminated disease present pulmonary affection, although in the localized variety it is rarely found in patients under 15 years of age.¹ These cases are associated with fever, dyspnoea and weight loss. From the evolutionary standpoint, sometimes cysts or bullae appear which, upon rupture, produce pneumothorax. In the final phase, emphysema and fibrosis can be observed.

Bone marrow: Pancytopenia is common in the disseminated variety of the disease. Patients with severe hematologic affection bear worse diagnosis, especially in cases where thrombocytopenia is present.

Central nervous system: Few patients present alteration of this system. Some signs are intracranial hypertension, trembling, dysarthria, hyperreflexia,

hemiplegia, quadriplegia, dysphagia with or without intellectual deficit.¹²

The characteristic disorder in this condition is diabetes insipidus due to hypothalamus-pituitary affection.¹

DIAGNOSIS

In cases when LCH is not borne in mind, variety of symptoms present and its rare occurrence might render diagnosis difficult. Clinical criteria might suggest presence of the disease, but histological confirmation is required in all cases.¹ Final diagnosis is attained with the help of lesion biopsy,¹⁶ (incisional, excisional etc). It is compulsory to observe with electron microscope in search of intracellular presence of Birbeck granules^{1,4,8,12} (rod shaped cytoplasm structures) or ascertain positivity in the immune-histochemical test of CD1 markers (antigen-presenting immunoglobulins) in the membranes of cells found in the lesions.^{1,2} In cases when the whole system is compromised, it is recommended to perform simple radiological study, computerized axial tomography (CAT) or magnetic resonance (MR) to confirm presence of bone and lung lesions.²

DIFFERENTIAL DIAGNOSIS

Bone lesions can present radiologic image similar to that of bone tumors and osteomyelitis. Skin lesions are many times mistaken for seborrheic dermatitis cases. When the whole system is compromised, with presence of hepatomegaly and splenomegaly, cases are often mistaken for leukemia and lymphoma.¹

The classical sign of LCH found in the jaws is the premature loss of teeth. In these situations, differential diagnosis must include juvenile or diabetic periodontitis, hypophosphatasia, cyclic neutropenia, agranulocytosis and primary or metastatic malignant tumors. Vitality in the affected teeth pulp precludes the possibility of apical granuloma or cysts.

Central and solitary radiolucent lesions in the jaws must be differentiated from odontogenic cysts and tumors. If a certain number of lesions are found, they can suggest a case of multiple myeloma, nevertheless, this condition is normally found in older patients.⁴ In all cases, diagnosis will be established through histological evidence.

PROGNOSIS

Prognosis is contingent upon three factors:

1. Age of patient when condition begins

2. Number of affected teeth
3. Organic dysfunction degree⁶

Children under two years of age at the moment when diagnosis is emitted present a higher mortality rate than those older than this age.

The development of untreated disease is extremely variable. LHC can spontaneously resolve, or it can disseminate, compromising visceral organs, with a resulting fatal outcome.¹

When deciding upon disease extension and severity, it must be borne in mind that the important fact is not the organ's lesion in itself, but rather the presence or absence of dysfunction in that organ.

When viscera are compromised, the prognosis is dimmer.⁸ There is linear correlation between mortality and the amount of affected organs. In cases when 1 or 2 organs are compromised, mortality reaches 10%. When three or more organs are compromised, mortality reaches 90% of cases.^{1,2}

Patients with bone located disease bear excellent prognosis. In these cases mortality is almost nonexistent.¹²

As a consequence of bone affection and depending on the lesion location, orthopedic and aesthetic alterations can be present.^{1,5}

TREATMENT

The International Histiocyte Society internationally classifies treatment into: Low, Intermediate or High according to risk of patients.

The following methods are included:

1. Surgical intervention
2. Radiotherapy
3. Chemotherapy

There is general consensus stating that surgical curettage is the treatment of choice for isolated bone lesions, and radio- and chemotherapy are reserved for lesions that cannot be accessed through surgery. It is of utmost importance to carefully select affected teeth to be extracted, since not all affected teeth must be treated in such an aggressive fashion. Only teeth presenting severe mobility and extensive lytic lesions are candidates for extraction.⁸

CASE REPORT

11 month old male patient (V.M.K.A.) referred to the emergency clinic of the Tamaulipas Children's Hospital (Hospital Infantil de Tamaulipas) due to a sus-

pected peri-tonsillar abscess. The patient presented a lesion in the mouth which warranted consultation with the Pediatrics- Stomatological Department.

The patient came from San Fernando, Tamaulipas, where his mother took him to the community health center. Medical reports of the aforementioned health center inform that the patient began showing symptoms one month before consultation. The patient presented hyaline rhinorrhea, non-assessed fever, volume increase in the submandibular and bilateral parotid region. The lesion was indurated and painful to palpation, emitted foul odor, there was a purulent blood discharge from the right ear, with epistaxis equally present. The mother informed of having administered several analgesic and antibiotic drugs to treat her son's condition.

Upon arriving at the ER of the Health Center, the patient was found to be irritable, with 38°C body temperature. CBC was taken which showed the following: Hemoglobin value of 8 mg/dL, leukocytes: 17,800 mmc, neutrophils :68.7%, lymphocytes 24.5% platelets: 297,000 mmc.

The patient's history was as follows: 24 year old mother afflicted with hypothyroidism, 6 year old male sibling suffering from asthmatic bronchitis, maternal grandmother afflicted with type II diabetes mellitus. The mother informed that in the family there had been three deaths of maternal grand-uncles, during childhood, due to neck lymphadenopathy.

CLINICAL EXAMINATION

The patient's apparent age matched chronological age.

Physical exploration showed erythematous, scaly skin lesions in the scalp, 3 cm³ lymphadenopathy in parotid and cervical regions. Lesion was indurated and painful to palpation;. Clinical observation showed absence of heat or blush, bloody and purulent discharge off the right ear, epistaxis and generalized foul smell of the patient (Figure 2).

Extraorally, lips appeared dehydrated. Intraorally no pathological clinical manifestations were observed in the tongue, floor of the mouth, hard and soft palate, anterior pillars, mucosa and retromolar area in cheeks. The following was equally observed: hypertrophic tonsils, active eruption of teeth number 5.2, 5.1, 6.1, 6.2, 7.2, 7.1, 8.1, 8.2. Teeth number 7.1 and 7.2 respectively presented 1st and 3rd degree mobility.

At tooth 7.2 location where tooth 7.3 was to erupt, a 3 cm³ purplish color volume increase was observed. In that region, the mass presented necrotic areas and was of a friable nature, where it extended to the back-



Figure 2. Upper photograph shows scalp erythematous, scaly lesions. Lower photographs shows cervical lymphadenopathy.

ground oral pouch and lingual portion. The patient also presented halitosis (Figure 3).

RADIOLOGICAL EXAMINATION

A lower occlusal x-ray was taken. In it, a well circumscribed radiolucent area was observed at the site of teeth number 7.2 and 7.3. There was no evidence of trabecular bone or root formation in the aforementioned teeth, which gave them a «floating teeth» appearance (Figure 4).

Due to the general systemic endangerment of the patient, he was admitted so as to perform biopsies and initiate treatment.

Clinicians at the Stomatological Department recommended cleansing with bicarbonate mixed in lukewarm water after meals at the site of the lesion, as well as



Figure 3. Upper picture shows lesion's clinical appearance on exploration day. Lower picture shows lesion appearance after 17 days.

in the whole mouth as temporary treatment until final diagnosis was emitted.

During the patient's stay at the hospital, laboratory analyses were undertaken. The following values were observed: severe anemia values HB 7 mg/dL, Hematocrit 21.1%, Leukocytes 12,700 mmc, Lymphocytes 42%, Neutrophils 55%, eosinophils 3%, platelets 40,000 mmc, Prothrombin time: 14.5 sec. Tissue Thromboplastin Partial Time : 24.8 sec.

A treble antibiotic scheme was initiated with the following drugs: Ceftriaxone, 365 mg, IV; Amikacin, 75 mg IV; Metronidazole 100 mg IV. The following drugs were also administered: diclofenac drops, 100 mg every 8 hours, ranitidine, 10 mg IV and sodium metamizole (sodium suphonate of aminopyridine) 180 mg IV.

After consultation with the genetics department, hereditary connection with the present state of the patient was precluded.



Figure 4. Occlusal x-ray showing lytic lesion at teeth 7.2 and 7.3 level.

In the operating theater, resection was made of the left inguinal ganglion (lymph). An incisional biopsy was taken of the oral mucosa lesion to perform histopathological analysis. The diagnosis emitted was Langerhans cell histiocytosis with inguinal lymph and oral mucosa compromise (*Figure 5*).

Once the diagnosis was established, chemotherapy treatment was initiated with Vinblastine 3.4 mg IV (6.5 mg 2 twice a day and Etoposide 26.5 mg IV (50 mg twice a day), during 2 cycles.

The patient experienced a general health improvement. The following was observed: volume decrease in cervical lymphadenopathy, lesser ear and nose discharge, in the mouth the lesion changed color: from purplish red it turned pink, extending still to the innermost location oral pouch and lingual portion. Necrotic areas had disappeared (*Figure 6*).

Tooth # 7.3 was actively erupting. This tooth presented 3rd degree mobility. Even teeth # 7.1 and 7.2 presented mobility.

During the period when chemotherapy was administered, the patient was afflicted with Oral Candidiasis. This condition could be observed in the cheeks mucosa and hard palate. Lesions had a whitish appearance which, when rubbed, came loose leaving an erythematous area. In this case, Daktarin gel[®] was administered as treatment. During this period the patient contracted chickenpox, which in the mouth manifested itself as ulcers in the pouch mucosa, at the level of tooth # 8.4. This situation was treated with Kaolin and Pectin, as well as Benadryl[®] mixed in equal parts, to be applied in ulcerated areas.

The patient was later afflicted with the following: abdominal distension, tachycardia and respiratory difficulties. Three times he required transfusions. The patient's clinical picture became more severe up to his



Figure 5. Sample harvesting and oral mucosa incisional biopsy cut with Pass Tincture. 40x



Figure 6. Clinical changes observed after chemotherapy administration.

demise after 41 days in hospital. The causes of death were deemed to be congestive cardiac insufficiency, pancytopenia, Langerhan s cell histiocytosis, probable intracranial hemorrhage and chickenpox.

DISCUSSION

Clinical characteristics of this patient were compared with results of a study conducted in 2002 by the National Institute of Pediatrics (INP), (Instituto Nacional de Pediatría).¹⁴ The following facts were observed:

The study mentions this condition afflicts children under one year of age. This was confirmed in the present case.

The present and the aforementioned study concur in the manner of disease presentation: affected organs

were skin (scalp) cervical and inguinal lymph nodes as well as the oral mucosa.

INP study states that the most frequent diagnostic anatomical site was bone, followed by lymph node (ganglion), and skin assuming the third place. In the present case, diagnosis was conducted in the inguinal ganglion and oral mucosa.

Treatment of the present case concurred with treatment reported in the INP study.

Hepatic and pulmonary dysfunction are associated with high mortality. The patient in our study presented those characteristics before his demise.

The aforementioned INP study states that all patients died in a time span shorter than 20 months, and this was directly associated to the condition. 100% of patients were under two years of age.¹⁴ Our case con-

curs in age of patient at time of death and evolution time of the disease, but differs in the sense that our patient additionally contracted smallpox.

Another relevant clinical manifestation when comparing with the INP article, is the fact that the patient presented a lesion in the mouth, in which the following clinical characteristics were observed: abnormal mobility of affected teeth, premature eruption of tooth # 7.3, volume increase in this area, which presented an unclean, friable appearance with necrotic areas. According to statistics presented in the INP article, this type of lesion is infrequent.

CONCLUSIONS

Langerhan`s cells Histiocytosis is a condition which can present different clinical pictures, according to the extension and severity of organic endangerment . This renders diagnosis difficult.

The patient` s case here described presented the same clinical manifestations as those described in INP study.

It is of paramount importance for the dentist to be more cognizant on LCH, since oral lesions can well be the first manifestation of the disease, and in many cases, the oral cavity can be the only affected site.

Due to the scarcity of cases, this condition is often ill-treated. Accurate diagnosis is based upon histological, radiographic and clinical examination. Final diagnosis will be based upon histological evidence.

When devising a treatment plan, it is of the utmost importance to take into account the patient`s general state of health, since it could prove to be a limiting factor.

The quality of life for Langerhans cells histiocytosis patients depends on the onset of the condition, general damage incurred, and administered treatment.

This case is an example of the disease aggressiveness and of the importance of early diagnosis to provide adequate treatment.

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