

Journal section: *Oral Medicine and Pathology*

Publication Types: *Review*

## Langerhans cell histiocytosis: Literature review and descriptive analysis of oral manifestations

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Madrigal-Martínez-Pereda C, Guerrero-Rodríguez V, Guisado-Moya B, Meniz-García C. Langerhans cell histiocytosis: Literature review and descriptive analysis of oral manifestations. *Med Oral Patol Oral Cir Bucal.* 2009 May 1;14 (5):E222-8.

<http://www.medicinaoral.com/medoralfree01/v14i5/medoralv14i5p222.pdf>

Received: 12/06/2008  
Accepted: 24/01/2009

Article Number: 111111858 <http://www.medicinaoral.com/>  
© Medicina Oral S. L. C.I.F. B 96689336 - pISSN 1698-4447 - eISSN: 1698-6946  
eMail: [medicina@medicinaoral.com](mailto:medicina@medicinaoral.com)

**Indexed in:**

- SCI EXPANDED
- JOURNAL CITATION REPORTS
- Index Medicus / MEDLINE / PubMed
- EMBASE, Excerpta Medica
- SCOPUS
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### Abstract

Langerhans cell histiocytosis (LCH) is a rare disease, of unknown pathogenesis, characterized by intense and abnormal proliferation of bone marrow-derived histiocytes (Langerhans cells). It can present both local and systemic manifestations involving bone, skin and mucosal tissue, and internal organs. Three basic clinical forms develop: Letterer-Siwe disease (subacute or acute disseminated form), Hand-Schüller-Christian disease (disseminated chronic form) and eosinophilic granuloma (localized chronic form).

LCH may manifest orally with single or multiple lesions of the alveolar or basal bone, ulcerated mucosal lesions accompanied by adenopathies and/or periodontal lesions, presenting gingival inflammation, bleeding, recession, necrosis, odontalgia, dental hypermobility and premature loss of teeth. The principal differential diagnoses include advanced periodontal disease or a periapical process of dental or periodontal origin.

The odontologist plays a vital role in the diagnosis and multidisciplinary treatment of such patients, by performing routine examinations for periodic follow-up of the disease and its possible oral manifestations, bearing in mind that these may be the first or only signs of LCH.

**Keywords:** *Langerhans cell histiocytosis, histiocytosis X, oral manifestations.*

## Concept

Langerhans cell histiocytosis (LCH) (formerly histiocytosis X) is characterized by intense and abnormal proliferation of bone marrow-derived histiocytes (Langerhans cells), together with a variable number of leucocytes, eosinophils, neutrophils, lymphocytes, plasma cells and giant multi-nucleated cells causing tissue destruction. This tissue destruction is a result of the cellular infiltration that replaces bone and invades skin, mucosa and internal organs (1-3).

Lichtenstein classified LCH into three clinical forms depending on the age of the patient when the lesions first appear and their distribution. Although other classifications have been proposed, this remains the most used in the literature, adding congenital reticulohistiocytosis described some years later.

- Chronic focal LCH (eosinophilic granuloma): is considered the most frequent and benign of the clinical forms. It appears as a uni- or multifocal lesion in a single, or occasionally various bones, with or without soft-tissue involvement, without systemic involvement and presenting at any age (3).

- Chronic diffuse LCH (Hand-Schüller-Christian disease): usually appears in children or young adults, with lesions that arise desynchronously over the years. It manifests with the characteristic triad of exophthalmos, osteolytic lesions of the cranium and diabetes insipidus. Other manifestations, petechiae, purpura, ulcerations, lesions mimicking seborrheic dermatitis, pulmonary dysfunction, tachypnea, dyspnea and cyanosis, may appear. This clinical form may imitate cystic lesions, leukemia, lymphoma, metastasis, meningioma, and congenital processes such as encephalocele (3, 4).

- Acute disseminated LCH (Letterer-Siwe disease): the patients are generally children under three years old, who, due to the aggressive behavior of the disease follow a fatal course in a short time. It manifests in multiple organs and systems, such as liver, lung, lymph nodes, skin, SNC, bone marrow and bone, finding variable manifestations such as eczema, hepatosplenomegaly, otitis media, anemia, hemorrhages, lymphadenopathies and osteolytic lesions (3, 5).

- Congenital reticulohistiocytosis (Hashimoto-Pritzker syndrome): believed to be a purely cutaneous form, characterized by the appearance of dark nodules on the trunk, face and scalp. The mucosae are always involved, without implication of other organs (6).

## Epidemiology

LCH is an infrequent disease. The relative incidence of LCH is not well known, due principally to the heterogeneous clinical expression, but is estimated at approximately 2-5 cases per million inhabitants per year, being more frequent between the first and third decades of life, although it may affect any age group. Eighty per-

cent of cases occur in Caucasians, with a predominance in males (1-3, 7).

## Etiopathogenesis

The pathogenesis of LCH is unknown, and various hypotheses have been proposed about its possible etiology. It may be caused by a dysfunction of the immune system, representing a hypersensitive reaction to an unknown antigen, with stimulation of the histiocytes-macrophage system (8,9). Deficiency of suppressor lymphocytes (T8), altered immunoglobins, autoantibodies, anomalous lymphocytic response to various mitogens and structural changes in the thymus in all the advanced forms have been found in LCH patients (7).

An inflammatory origin is also suspected due to the microscopic characteristics and clinical evolution; or a bacteriological origin, although no specific causal microorganisms have been identified (8,9).

The systemic alterations presenting in these patients result from the accumulation of Langerhans cell infiltrate that produces different clinical manifestations depending on the location (10).

## Oral manifestations of LCH

Oral manifestations may be the first sign of LCH, and on some occasions the oral cavity may be the only area affected (11). The incidence of oral lesions in LCH is 77% (7), therefore the initial diagnosis in many cases is made by the odontologist. For a more detailed description, we have classified these lesions into bone, mucosal and periodontal.

- *Bone lesions.* Alongside the cranium, the maxilla and mandible are the most affected bones, usually infiltrating together. Mandibular lesions are clearly more frequent in all three forms of LCH (1).

Dagenais et al. (2) in a review of 29 cases of LCH found the majority of bone lesions presented in the posterior section of the mandible (distal and canine region) and in the ramus of mandible. When osteolysis is found in the anterior area of the mandible it is as an extension of the posterior. They also observed that when two or more lesions are present, these are always located in the alveolar ridge, finding different forms of bone loss even within the same patient. The different types of lesions produced by LCH in the maxilla and mandible are described according to their radiographic characteristics (1,2).

- *Solitary intra-bony lesions:* localized outside the alveolar process, these are the most frequent in the initial phases. The images are circular or elliptical, solitary or unifocal, found principally in the body and ramus of mandible. They may be obvious and painful, causing facial swelling, or they may be asymptomatic being an incidental radiographic finding.

- *Multiple alveolar lesions:* normally present with well-

defined though not corticalized margins. However, 37.7% of alveolar lesions may have poorly-defined or invasive margins.

- ‘Scooped-out’ alveolar lesions: formed by bone destruction beginning below the alveolar crest, either at furcal level or at half the tooth root height and normally a part of the coronal portion of the bone crest remains intact on the mesial and/or distal margin of the damaged bone. This form of intra-bony destruction is not seen in periodontal disease, and may therefore be useful in a differential diagnosis.

- Alveolar lesions with bone sclerosis: common in inflammatory lesions of the jaws, the fact that sclerosis appears in alveolar lesions in LCH may be explained by the communication of these with the oral cavity with added infection. Thus, intra-bony lesions do not present sclerosis as they do not communicate with the oral cavity.

- Alveolar lesions with bone neoformation: formation of new bone in lesions classified as intra-bony is observed in a high number of cases. This is a relevant characteristic when differentiating LCH lesions from those of periodontal disease.

- *Mucosal lesions.* These are ulcerated, ovoid or round lesions, with erythematous, inflamed borders, painful on palpation (Fig. 1). They are localized principally in the buccal mucosa and at the back of the vestibule. They are associated with cutaneous lesions such as the typical eczematoid rash, that may be confused with a sebaceous dermatitis. Occasionally subcutaneous nodules present, therefore the initial evaluation of the patient should also include a meticulous skin examination (12).

Some unusual cases of oral soft tissue lesions in the absence of bone lesions have been described (1). The mucosal lesions are usually accompanied by enlargement of the lymph nodes which also reflects the degree of histiocytic infiltration. Thirty percent of patients with oral lesions present cervical lymphadenopathies (7).

- *Periodontal lesions.* Alveolar bone lesions form the basis for all the associated periodontal involvement in these patients. As new osteolytic areas develop, accompanying gingival ulceration and inflammation are observed, such that all the quadrants of the oral cavity are affected to a greater or lesser degree, even though the process began initially in only one quadrant. Dagenais et al. (2) observed slight radicular resorption associated with these lesions in 53% of cases studied, seen in the retro alveolar radiographies as images typical of a periodontal lesion (1).

As a consequence of the alveolar bone loss, these patients manifest gingival inflammation, ulceration, destruction of the keratinized gingiva, gingival recession, periodontal pockets and bleeding of the oral soft tissues, associated with pain and even swelling (Fig. 2). As a result of this loss of bone support the teeth begin



Fig. 1. Ulcerated lesions in the buccal mucosa.



Fig. 2. Periodontal lesions with inflammation, recession and tooth mobility.

to progressively move giving rise to the characteristic ‘floating teeth’, completely surrounded by a radiolucent defect accompanied by dental displacement, odontalgia and on occasions cervical adenopathies. This excessive mobility gives rise to the inevitable premature loss of these teeth (3, 7, 10).

The general and oral manifestations and the treatments established in cases of LCH published by the different authors reviewed (4-6, 13-19) are summarized in Table 1.

### Diagnostic and complementary examination

The diagnosis is confirmed by histological study supported by clinical and radiographic examination. Biopsy by conventional microscopy shows areas of conjunctive fibrous tissue related with a mixed inflammatory infiltrate. Non-malignant histiocytic proliferation is seen together with the Langerhans cells (with Birbeck granules). These large mononuclear histiocytic cells are round or oval in shape, with a vesicular nucleus, a moderate quantity of eosinophilic cytoplasm, and lami-

Table 1. Cases Of Lch With Oral Manifestations.

DATE / AUTHOR	AGE/SEX	GENERAL MANIFESTATIONS	ORAL AND BONE MANIFESTATIONS	TREATMENT
1988 Shaw L. and Glenwright HD (5)	6 Male	Submandibular lymphadenopathy. Interstitial changes with histiocytic infiltrate in breast.	Bleeding, pockets and bone loss in the lower incisors.	Tetracycline 250 mg, 2 v/d 2 m. Surgical curettage and chemotherapy.
1989 Artzi Z et al. (13)	32 Male	Alteration in thyroid glands and external otitis. Multifocal non bony nodule in head and neck.	Supragingival calculus in 31, 32 and 41. Bone loss in 31 and 41. Submaxillary glandular involvement. Ulceration and Erosion. 5 mm-diameter lesion. Bony lesions in occipital region and pelvis.	Excision of submaxillary glands. Hemithyroidectomy. Chemotherapy.
1996 Cleveland DB et al. (14)	63 Male	Diabetes. Hypertension.	Ulcerated areas in buccal maxillary gingiva. 16 and 37 in poor periodontal condition. Circumscribed unilocular radiolucent lesion in mandibular canine/premolar area.	Insulin and hypotensor. Extraction of 16 and 37. Excision of lesional tissue.
2001 Milián M et al. (6)	34 Female	Diabetes insipidus.	Ulcers in mucosa of hard palate.	Not treated.
	60 Male	Hypertension.	Red and white lesions in mucosa anterior mandibular vestibule. Edentulous mandible. Upper teeth in poor periodontal condition.	Hypotensor.
	50 Male	Urolithiasis, hiatus hernia and diabetes mellitus.	Ulcer 1 cm in hard palate with non indurate margins and clean base. Teeth and periodontium without pathology.	Oral Hypoglycemics. Triamcinolone acetonide (25 mg; one injection every 3 weeks. 8 sessions).
2001 Loducca SVL et al. (15)	52 Female	No manifestations.	Painful ulceration in lingual area of 36.	Radiotherapy.
2002 Muzzi L et al. (16)	10 Female	Bony lesions in cranium	Radicular exposure and mobility of 36. Inflamed gingival tissue and granulomatosis.	Chemotherapy. Extraction of 36.
2002 Becelli R et al. (4)	24 Female	Pulmonary anomalies.	Periodontal lesions in lower molar regions. Pain, burning sensation and bleeding.	Vasopressin.
	61 Female	Splenomegalia. Cutaneous Eruptions. Right otorrhea. Multiple osteolytic lesions in right mastoid apophysis, scapula, iliac crest, tibia, occipital and sphenoids. Eczema parietal region. Lymphadenopathies. Osteolytic lesions in scapula and cranium.	Pain in both jaws. Swelling of maxillary region. Osteolytic lesions in mandible.	Surgical curettage of lesions.
2005 Mitomi T et al. (17)	3 Female	Otitis. Cutaneous lesions behind and within the auricular cavity. Cough with dyspnea. Diabetes insipidus.	Bleeding gingiva in molar region. Demineralized lower teeth and bone resorption. Osteolytic lesions in mandible extending toward condyles.	Chemotherapy.
2005 Manfredi M et al. (18)	23 Male	Low levels of some hormones such as GH.	Painful ulcerations in molar region. Pain, burning sensation and spontaneous bleeding.	Amoxicillin. Chemotherapy and corticosteroids.
2005 Nakamura S et al. (19)	31 Male		Red and white staining of lower left molars. Pain and bleeding at lower 2 <sup>nd</sup> PM and 1 <sup>st</sup> M.	Antibiotic therapy. Radiotherapy.

nated or dispersed distribution. Abundant eosinophils and other inflammatory cells such as lymphocytes and mononuclear phagocytes may be found accompanying these cells.

Electron microscopy reveals Birbeck granules in the lesional cells, described as organelles with rod-shaped or tennis-racket morphology that could represent structural changes of the membrane following contact with an antigen. The percentage of histiocytes with Birbeck granules is not related with prognosis. Using immunohistochemical techniques, the mononuclear histiocytic cells show positive to markers S-100 and/or CD1A, and demonstrate ATPase activity of the cellular membrane (6, 20-22).

The biopsy is similar in all LCH except in the acute disseminated form, as this may demonstrate microscopic findings of other diseases, such as acute forms of lymphoma.

There are no specific laboratory tests for LCH, however, blood and urine tests exist that reveal the extent and seriousness of the disease. Routine laboratory analyses, liver function tests and coagulation tests are made.

Imaging studies include X-ray of thorax, computed tomography (CT) and magnetic resonance imaging (MRN) of the affected areas, with the aim of delimiting the bone and soft tissue lesions. CT is useful to evaluate the cranium and facial bones, which are difficult to visualize in conventional radiographies (23). Bone scintigraphy is indicated to evaluate multiple involvement and to discard polyostotic disease. This test will show hyperuptake in affected bone (6).

In the presence of oral manifestations, orthopantomograph, intraoral radiography and even maxillofacial CT

are necessary to localize and delimit lytic lesions in any of the previously-described forms. Given the periodontal and bone characteristics of LCH, noninfectious bone loss associated with ‘floating teeth’ should be included in the differential diagnosis. Furthermore, alveolar and periodontal lesions could produce an erroneous diagnosis of advanced periodontal disease, or have similar appearance to a periapical process of dental or periodontal origin (1, 3, 24, 25).

When the process is located also in the oral mucosa the differential diagnosis should be made with sarcoidosis and diseases that present giant cells in the histology. The differential diagnosis of oral manifestations and lesions of LCH includes the pathologies described in Table 2 (1, 6, 14).

**Prognosis and treatment**

The prognosis of LCH is difficult to assess since this is a rare disease with high clinical variability. In the majority of patients LCH is a self-limiting process, although often with alternating phases of relapse and remission. The course of the disease is unpredictable and can evolve with multiple reactivations (7). The most important factors that may worsen the prognosis are firstly, visceral involvement (liver, lung, bone marrow), as this has a negative effect on survival. Secondly, where age at first presentation is less than two years since mortality rises to 50%. Thirdly, when the disease spreads to various bones or soft tissues. In general, it is considered that the younger the patient, the worse the prognosis (1, 3). A multidisciplinary evaluation is vital for correct diagnosis and treatment for these patients. Diverse therapeutic options are available, and there is no consensus on

**Table 2.** Differential diagnosis of LCH.

ORAL LESIONS	Advanced periodontal disease.		
	MULTIFOCAL LCH	<b>Periapical abscess.</b> Osteomyelitis. Ewing’s sarcoma. Brown tumor hyperparathyroidism. Multiple odontogenic keratocyst. Multilocular cyst. Leukemia. Lymphoma.	
	UNIFOCAL LCH	CHILDREN	Metastatic neuroblastoma. Intrabony hemangioma. Fibrous dysplasia. Hemophilic pseudotumor. Epidermoid cyst. Giant cell granuloma
ADULTS		Osteolytic metastasis. Multiple myeloma. Myxoma. Ameloblastoma. Osteogenic sarcoma. Fibrosarcoma.	

the best treatment combination, although the measures taken will depend on the location and extent of the lesions (10). Antibiotic therapy, chemotherapy, radiotherapy, surgery, Adrenocorticotropic hormone (ACTH) and corticoids (both systemic and intralesional) are used.

Treatment of LCH is constrained both by the natural history of the disease as well as the location and extent of the lesions and the degree of organ dysfunction. Occasionally different therapeutic approaches are required in response to changes in behavior of the disease.

Unifocal bone lesions do not usually require any therapy since they can resolve spontaneously, while multifocal lesions or disseminated disease may require the combination of various types of therapy, including surgical curettage. Some authors suggest treatment with low-dose radiotherapy in large or multifocal lesions that recur or progress after surgery, in lesions carrying risk of fracture, lesions inaccessible to surgery, painful or disseminated lesions, or in those occurring in the ossification centres of the mandible during infancy. Doses of 600 to 1000 cGy in 3 to 5 sessions seem to achieve local control in the majority of these patients. Its use has decreased as it damages the permanent dental follicles and there is a risk of developing malignant lesions, especially in children, reserving therapy for large recurrent lesions (1, 15).

Systemic chemotherapy should be used in more diffuse lesions, untreatable by surgery, and when local treatment is unsuccessful in localized disease or in multi-systemic disease. Recently, the epipodophyllotoxin etoposide (VP16) has emerged as one of the most active and least toxic chemotherapies (6, 26).

According to Zhang et al. (12) these patients should be treated surgically and only complemented with a low-dose radiotherapy and/or chemotherapy in serious cases, especially in disseminated forms.

Localized and isolated mandibular lesions may be efficiently treated by surgical curettage. When surgery leaves large bony defects, autologous bone grafts can be made in an attempt to reduce the risk of pathological fracture and to facilitate bone regeneration (26).

Intralesional corticosteroids may be administered for the monostotic acute form. Triamcinolone acetonide or methylprednisolone sodium succinate are used (27, 28). In cases of LCH with oral manifestations, it is unnecessary to extract all the teeth involved in the process, only those with marked mobility, or with periapical lytic lesions and those presenting symptomatology. Correct mucosal and periodontal treatment involves tartar removal, and radicular scaling and planing, as well as rigorous hygiene and maintenance to conserve both teeth and periodontal tissue.

It is therefore essential that the odontologist, as part of a multidisciplinary treatment approach, carries out routine examinations and long term control of these pa-

tients for the periodic follow-up of the disease and its possible oral manifestations, bearing in mind that these may be the first or only signs of LCH.

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