

# Oral Manifestations of Chronic Disseminated Langerhans Cell Histiocytosis: A case report

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## ÖZET

**Kronik dissemine langerhans hücreli histiositozis'in ağız bulguları: Bir vaka raporu**

Histiositozis X, histiosit-türevi hücrelerin proliferasyonu ile karakterize klinik-patolojik bozukluk spektrumunda kolektif bir terim olarak tanımlanmıştır. Bu lezyonda gösterilen tipik histiositik hücreler Langerhans hücreleri olarak tanımlanmış ve bu durum Langerhans hücre histiositozis olarak gösterilmiştir. Kronik yayılmış Langerhans hücreli histiositozis kemik, deri ve iç organları içine alan bir hastalıktır (Hand-Schüller-Christian hastalığı). Kronik yayılmış Langerhans hücreli histiositozis triadı- kemik lezyonları, ekzoftalmi ve diabetes insipidus- kronik yayılmış hastalıkların çok azında gözükür. Kronik yayılmış hastalıkta sıklıkla morbidite görülür, fakat hastalık yüzünden az sayıda ölümle sonuçlanır. Bu çalışmanın amacı 34 yaşındaki erkek hastada görülen Kronik yayılmış Langerhans hücreli histiositozis hastalığını sunmaktır. Klinik muayeneye ek olarak hastaya medikal, panoramik ve histolojik inceleme yapılmıştır. Radyolojik ve histolojik dental pratikte önemlidir ve klinisyenler dental ve mukozal anomalilerin varlığında dikkatli olmalıdır.

**Anahtar sözcükler:** Langerhans hücresi, Kronik yayılmış Langerhans hücreli histiositozis, sintigrafi

## ABSTRACT

**Oral manifestations of chronic disseminated langerhans cell histiocytosis: a case report**

The term histiocytosis X was introduced as a collective designation for a spectrum of clinopathologic disorders characterized by proliferation of histiocyte-like cells. The distinctive histiocytic cells present in this lesion have been identified as Langerhans cells, and the condition is now designated as Langerhans cell histiocytosis. Chronic disseminated langerhans cell histiocytosis is a disease involving bone, skin, and viscera (Hand-Schüller-Christian disease). The often-cited Chronic disseminated langerhans cell histiocytosis triad (bone lesions, exophthalmos and diabetes insipidus) is present in only a few patients with chronic disseminated disease. Chronic disseminated disease is often associated with considerable morbidity, but few patients die as a result of the disease. The aim of this report is to present a case of Chronic disseminated langerhans cell histiocytosis in a 34-year-old male patient. In addition to clinical examination, the patient was imaged using medical and panoramic examination; and histological examination was performed. Radiological and histological examinations are important in dental practice and clinicians must be watchful of the presence of dental and mucosal abnormalities suggesting the presence of systemic disorders.

**Key words:** Langerhans cells, Chronic disseminated langerhans cell histiocytosis, scintigraphy

## INTRODUCTION

Langerhans cell histiocytosis (LCH), is a rare disease characterized by a proliferation of Langerhans cells or their precursors (1,2). It is estimated that the disease occurs at the rate of 0.2 to 0.5 cases per 100.000 children per year. The skull, mandible, ribs, vertebra, and long bones are involved. Head and neck lesions are common and 10% of all patients have oral lesions (3,4).

The etiology and pathogenesis of LCH remain obscure. It is thought that the disease may result from exuberant reaction to an unknown antigenic challenge (5,6). A deficiency of suppressor T cells, as well as low levels of

serum thymic factor, suggest the presence of a thymic abnormality in LCH (6,7). Histologically, LCH is characterized by the proliferation of large cells with abundant cytoplasm, indistinct cell borders, and oval to reniform nuclei. These cells are most often arranged in sheets and may be admixed with various numbers of eosinophils and other inflammatory cells. Multinucleated giant cells and foci of necrosis may be noted. Langerhans cells cannot be differentiated from other histiocytes by routine histological staining; therefore additional histological diagnostic methods are needed. Using immunohistochemistry, the mononuclear histiocytic cells CD1a, S-100 and langerin (CD207) can be detected (1,2,8,9). This condition has been described as a neoplastic

process because of the monoclonal proliferation of LCs, as LCHCs express many LC antigens like CD1a, S-100 and langerin (CD207); more recent studies highlight the possibility that LCH is the result of an immune dysregulation (2,8).

The disease has been classified by Lichtenstein depending on the patient's age at onset and distribution of the lesions as follows: Eosinophilic granuloma (chronic focal LCH), which refers to solitary or multiple bone lesions with no extra-skeletal involvement; Chronic disseminated Langerhans Cell histiocytosis (Chronic disseminated LCH) (Hand-Schüller-Christian disease), which is a specific clinical triad of lytic bone lesions, exophthalmus, and diabetes insipidus; Letterer-Siwe disease (acute disseminated LCH), which is a malignant form of LCH (6,10).

The oral changes are the first clinical signs in all forms of LCH and on some occasions the oral cavity may be the only affected area (11). The incidence of oral lesions in LCH is 77% (6); therefore patients suspected of having the disease should be referred to an odontologist. Tenderness, pain and swelling are common patient complaints. The gingival tissues are inflamed, hyperplastic, and ulcerated. Ulcerative or a proliferative gingival mass may develop if the disease destroys the bone. The jaws may exhibit solitary or multiple radiolucent lesions. Bone lesions with a sharply circumscribed, punched-out appearance may occur in the central aspect of the mandible or maxilla. The lesions often affect the alveolar bone. In alveolar lesions the bone around teeth is destroyed, as a result, the begin to move progressively giving rise to the characteristic 'floating teeth', completely surrounded by a radiolucent defect accompanied by dental displacement, odontalgia and on occasions cervical adenopathies (12,13). Alveolar and periodontal lesions may resemble a periapical process of dental or periodontal origin (6,14,16).

The diagnosis is confirmed by histopathological examination supported by clinical and radiographic examination. Although there is not a specific laboratory test for LCH, blood and urine tests reveal the extent and seriousness of the disease (6). X-ray of thorax, computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy are useful to evaluate the affected areas of the bone and soft tissues (6,15,16,14,15). Panoramic radiography, intraoral radiography and even maxillofacial CT are necessary to localize and delimit lytic lesions in any

of the previously-described forms (6,14). Bone scintigraphy of the whole body is indicated to evaluate multiple involvements and to discard polyostotic disease. The result of this test will show hyperuptake in affected bone (6,15). 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 (6,16). Treatment options are surgical management, chemotherapy, radiation therapy and combinations of these modalities (4).

Chronic disseminated LCH usually appears in children or young adults. It manifests with the characteristic triad of exophthalmos, osteolytic lesions of the cranium and diabetes insipidus. The aim of this report is to present a case of Chronic disseminated LCH in a male patient.

## CASE REPORT

A 34-year-old male was admitted to the Department of Oral Diagnosis and Radiology, Marmara University, Faculty of Dentistry, Istanbul, Turkey suffering from a painful and non-bleeding palatal swelling for 3 months. The medical history revealed that diabetes insipidus was diagnosed 5 years ago and treated with desmopressin acetate (DDAVP). In addition, the patient reported to be suffering from osteoporosis and was treated with calcium. The family history was unremarkable.

The intraoral examination revealed an exophytic large ulcerative mass with an irregular and pebbled surface of the palatal mucosa (Fig. 1). Severe bone loss appeared in the maxillary molar regions on panoramic radiograph (Fig. 2). Antero-Posterior (AP) and lateral radiographic views of the skull revealed a slight lytic appearance on the right parietal bone (Figure 3). Routine blood tests, alkaline phosphatase (ALP), calcium, phosphorus, parathyroid hormone (PTH) and calcitonin levels were normal. An incisional biopsy of the mass was performed under local anaesthesia and the specimen was sent for histopathological examination to the Department of Oncologic Cytology and Tumor Pathology, Institute of Oncology, İstanbul University. Histopathologic features revealed an infiltrate of lymphomonocytes together with eosinophilic and neutrophilic



**Figure 1:** The intraoral examination revealed an exophytic large ulcerative mass with an irregular and pebbled surface of the palatal mucosa.

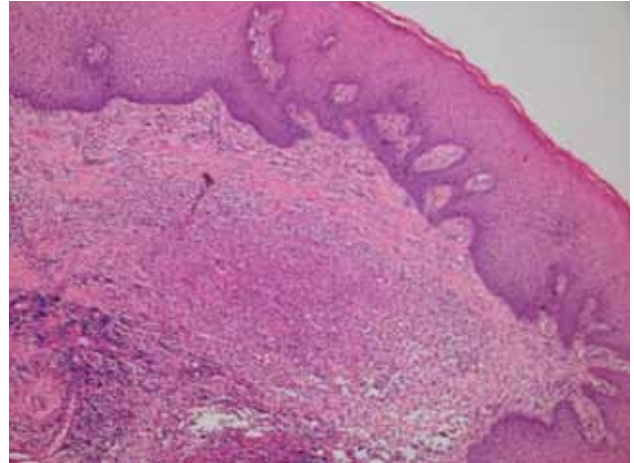


**Figure 2:** Panoramic radiograph showed severe bone loss in the maxillary molar regions.

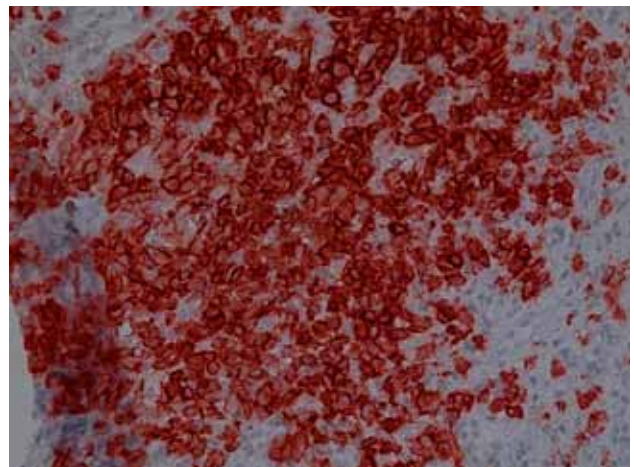


**Figure 3:** Antero-posterior and lateral radiographic views of the skull revealed a slight lytic appearance on the right parietal bone.

cells. The identification of lesional Langerhans cells was necessary to confirm the diagnosis. The diagnosis was confirmed by immunohistochemistry techniques (CD1a) (Fig. 4, 5). The histopathologic diagnosis was Langerhans cell histiocytosis. Chronic disseminated LCH term was given



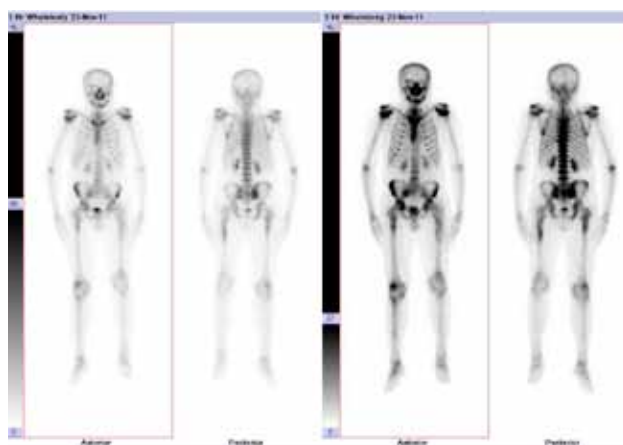
**Figure 4:** Microscopic appearance of Langerhans cell histiocytosis. Beneath the surface epithelium, infiltration of Langerhans histiocytes, lymphocytes and eosinophilic granulocytes are observed in the connective tissue (H&E, x100).



**Figure 5:** Langerhans histiocytes are positively stained with CD1a immunohistochemically (CD1a, x400).

to Langerhans cell histiocytosis causing exophthalmos, diabetes insipidus and lytic skull lesions. Therefore, clinical and histopathological diagnosis of Chronic disseminated LCH was done in this patient.

Due to the histopathological report, the patient was examined with technetium scintigraphy and bone SPECT to evaluate any bone involvement. Anterior and posterior projections of bone scan using technetium (Tc)-99m-labelled methylene diphosphate showed multiple foci of intense activity on right parietal bone of cranium, mandible and right femur (Fig. 6); therefore, the patient was referred to the Faculty of Medicine.



**Figure 6:** Anterior and posterior projections of bone scan using technetium (Tc)-99m labelled methylene diphosphate showed multiple foci of intense activity on right parietal bone of cranium, mandible bone and right femur.

## DISCUSSION

Chronic disseminated LCH is an infrequent disorder of childhood (13). The approximate incidence is one case in every 3,300,000 individuals (17). The disease usually appears in the first decade of life, with no particular sex predilection (13). In our case report the patient was a 34 year old. The lesion was an exophytic large ulcerative mass with an irregular and pebbled surface of the palatal mucosa and radiographic examination revealed severe bone loss in the maxillary molar regions. The most commonly affected bones are skull and facial bones, the femur, ribs, vertebrae and humerus (13). Thus, this lesion is similar to those described in the literature (8,11,16).

Chronic disseminated LCH has classically been defined as a triad comprising diabetes insipidus, exophthalmos and bone alterations, though only 25% of patients present the full picture (13,17), and according to Garcia-Pola et al. (18), the complete triad is actually found in less than 10% of cases. Similarly, Minguez et al. (13) observed that only in one of their patients the full triad was identified, while two patients presented two of the alterations (3 with bone lesions and diabetes insipidus, and 2 with bone lesions and exophthalmos). In our case, like the other studies (13,18), we identified two of the alterations (bone lesions and diabetes insipidus).

The diagnosis of LCH is based on histological and immuno-phenotypic examination of a biopsy of lesional tissue in addition to clinical and radiological features (19).

LCH is characterized by the proliferation of large cells with abundant cytoplasm, indistinct cell borders, and oval to reniform nuclei. These cells are most often arranged in sheets and may be admixed with various numbers of eosinophils and other inflammatory cells. In addition, macrophages, multinucleated giants cell and foci of necrosis may also be noted. The ultrastructure of tumor cells shows unique, rod-shaped cytoplasmic structures, which are identical to Birbeck granules, present in normal Langerhans cells (20). In immunohistochemical stains, CD1a, S100 protein and Langerin (CD207) are three markers widely used for identifying Langerhans cells (21). Electron microscopy is no longer recommended since it has been shown that the expression of Langerin (CD207) fully correlates with the presence of Birbeck granules on electron microscopy, which was previously one of the criteria required for definitive diagnosis (19). It should be noted that CD1a is a specific marker for normal Langerhans cells and the pathologic cells in LCH. The monoclonal antibody reactive to CD1a is effective for immunohistochemical analysis of formalin-fixed tissue, replacing the less specific S100 protein for confirmation of LCH (20). Our data showed that this case, immunostained with CD1a, was strongly positive with the markers. This finding demonstrates that LCH can be simply diagnosed histologically by the oral pathologists, and the use of immunostaining with CD1a aids in confirming the diagnosis.

Diagnosis should be based on clinical-radiological-pathological evidence. The classic presentation of LCH in jaws often results in loosening or premature exfoliation of teeth and precocious eruption of permanent teeth. A differential diagnosis should include juvenile or diabetic periodontitis, hypophosphatasia, leukemia, cyclic neutropenia and metastatic malignant neoplasms under these conditions. Lesions located in periapical site may mimic a periapical cyst or granuloma. Solitary radiolucent lesions in the central aspects of the jaws should be differentiated from odontogenic tumors and cysts and numerous well-circumscribed radiolucencies may suggest multiple myeloma (19,20).

The most widely used treatment options comprise chemotherapy, radiotherapy, surgery and corticotherapy. Diverse therapeutic options are available and no consensus exists over the best treatment combination. Treatment of LCH is constrained both by natural history of the disease as



well as the location and extent of the lesions and degree of organ dysfunction. Occasionally different therapeutic approaches are required in response to changes in behaviour of the disease (6,13,22). The combination of chemotherapy and systemic corticosteroids is the most often prescribed treatment approach, with dose variations according to the outbreaks of the disease (13). The Histiocyte Society performed three major study protocols for paediatric LCH (LCH-I, LCH-II, LCH-III); and more recently, a protocol for adult onset was started, considering vinblastine plus prednisone for multisystem disease, but the therapy regimen for adults still remains dubious: it can vary from watchful waiting to local therapy (surgery and radiotherapy) to systemic chemotherapy (cladribine,

thalidomide) in the refractory cases (1).

The prognosis of LCH is difficult to assess since this is a rare disease with clinical variability. The most important factors that may worsen the prognosis are firstly, visceral involvement, as this has a negative effect on survival; secondly, where age at first presentation is less than two years since mortality rises to 50%; and thirdly, when the disease spreads to various bones or soft tissues (6,12).

In conclusion, the management of long-term sequelae is not specific to LCH and all therapeutic options, like growth hormone therapy, and radiological and histological examinations are important in dental practice; and clinicians must be watchful of the presence of dental and mucosal abnormalities.

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