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CASE REPORT

# Unrecognized oral manifestations of Langerhans cell histiocytosis which progressed to systemic disease

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**Summary** A 2.5 years old boy was referred to the Department of oral medicine because of substantial erythema and ulcerations on palatal, buccal and alveolar regions. Unfortunately, it took two subsequent visits to our Department in six-months intervals, and re-evaluation at Pediatric oncology clinic where diagnosis of Langerhans cell histiocytosis (LCH) was finally established. At that stage, disease already progressed to multisystem life-threatening presentation, requiring aggressive treatment. Therefore, this case is a reminder of the possibility of occurrence of this rare disease in the oral cavity which might manifest itself in multiple presentations thus easily leading to the misdiagnosis and therefore it could be easily overlooked by dentists.


## Introduction

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X is a rare proliferative disease of histiocytes which may affect single system at single/multiple site or may represent itself as a multisystem disease. The disease usually occurs during childhood and the incidence is one case per 200 000 children per year, but it may also occur later in life.[1] Etiology is unknown and various theories suggest a role for environmental, infectious, immunologic, genetic causes, and even some believe that LCH is a neoplastic process.[2] The main

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feature of LCH is the abnormal proliferation of the antigen-presenting Langerhans cells (LC).[1] Immunological abnormalities resulting from a suppressor cell deficiency have been suggested as a cause, explaining the LCH as pathologic phenotype LCs production and action.[2] New data suggest that the abnormal immunological response may be the result of a viral infection of the lymphocytes, with special reference to HHV-6.[3] Recent case report describes regression of pulmonary LCH following excision of lingual carcinoma, ascribing paraneoplastic mechanisms to the case.[4] The diagnosis is based on the histopathological finding of dense infiltrates of large cells with eosinophilic cytoplasm and characteristic indented ovoid nuclei: Langerhans' cells together with histiocytes, eosinophils, lymphocytes and giant cells. These LCs have cytoplasmic inclusions known as ''Birbeck's granules'', visible on electron microscope. Confirmed diagnosis of histiocytosis comprise of cytoplasm staining of Langerhans' cells with S-100 protein, peanut lectin, and cell membrane staining with CD1a.[5] Radionuclide bone scan is valuable in the diagnostic process.[6] Spontaneous healing has been described throughout the literature as well as worsening concomitantly to various treatments.[7]

In cases where localized lesion is found surgical curettage is indicated, although other therapeutic approaches such as oral, topical and intralesional steroids were reported to be useful with various improvement results.[7] Where multiorgan disease is present most lesions disappear after chemotherapy and administration of systemic corticosteroids. In some affected bone marrow allografting, hematopoietic stem cell transplantation, PUVA phototherapy have been successful.[6]

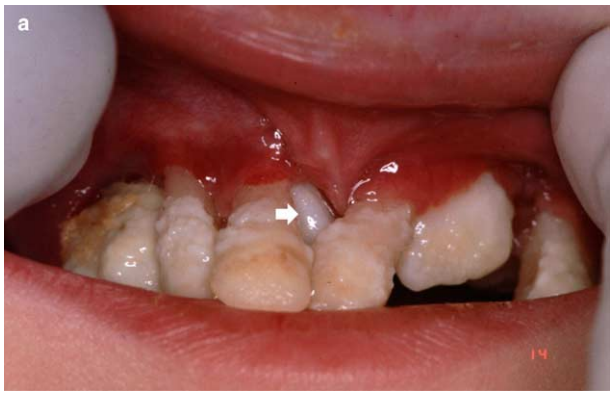


**Figure 1a** Disease caused alveolar bone lysis: a crown of permanent upper right first incisor (arrow) can be observed behind mobile deciduous first incisors with exposed root surfaces.

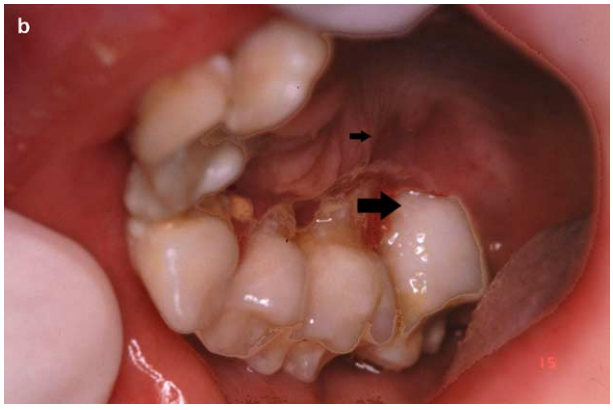


**Figure 1b** Palatodistal aspect of upper dental arch: inflammed and necrotic soft tissue, with exposed roots of deciduous molar teeth (small arrow) and precocious eruption of permanent first molar (large arrow).

## Case report

A 2.5 years old boy was referred to our Department at the School of Dentistry because of oral pain and inflammation that prevented regular foods and liquids intake. Oral findings showed substantial erythema and ulcerations on palatal and alveolar regions of both maxilla and mandible as well as on the buccal mucosa. Complete blood count and immunological laboratory tests (peripheral blood lymphocyte immunophenotyping, blastic transformation of lymphocytes) and serology for polio and *B. pertussis* showed normal findings. Six months later symptoms worsened and besides multiple oral ulcerations, changes in his dentition were present. Oral findings included generalized gingival inflammation with exposed roots of mobile deciduous teeth. Bone lysis had caused revelation of crowns of permanent maxillary incisors and mandibular molars, resembling precocious eruption of permanent dentition (Fig. 1). Panoramic radiograph showed horizontal bone loss.

At the age of four, patient's overall condition worsened progressively. He was admitted to pediatric clinic with acute clinical findings and symptoms. The boy was weak, highly febrile (39.8 °C) with tachycardia and stomach ache. Patient's skin was pale with diffuse maculopapulous rash on trunk and axillar pits. None of the lymph nodes were palpable. His teeth were mobile and he had frequent gingival bleeding. Oral findings included palatal and buccal necrotic ulcerations, coated tongue and dry mouth. Deciduous teeth roots and permanent teeth crowns were further exposed. His liver

was palpable. Laboratory findings showed marked anaemia (RBC $3.97 \times 10^{12}$/l (normal range 4.4–$5.8 \times 10^{12}$/l, Hb 103 g/l (normal range 119–157 g/l), Htc 0.30 l/l (normal range 0.356–0.470 l/l), trombocytopenia (Plt $110 \times 10^{9}$/l, normal range 158–$424 \times 10^{9}$/l), leucocytosis (WBC $21 \times 10^{12}$/l, normal range 3.5–$8.0 \times 10^{12}$/l) with lymphocytosis (Ly 81%). Transaminases were increased (AST 283 U/l, normal range 8–26 U/l; ALT 365 U/l, normal range 8–34 U/l, γGT 270 U/l, normal range up to 38 U/l), as well as lactate dehydrogenase (1359 IU/l, normal ranges 24 ± 195 IU/l), ferritin (581.29 ng/ml, normal range 12–300 ng/ml) and C-reactive protein (17.3 mg/l, normal range up to 6 mg/l). Bone marrow aspiration tests showed normal values, but cytopathologist noted ''numerous solitary cells and clusters of cells resembling histiocytes next to stroma''.

Skin lesion biopsy showed dermal histiocyte infiltration (CD1a staining). 99mTc MDP bone scan showed higher radionuclide concentration in saggital sinus of parietal bone, idicating skull involvement. Abdominal ultrasound confirmed hepatosplenomegaly. Peripheral blood immunophenotyping this time showed markedly decreased CD4 (helper), and markedly increased CD8 (cytotoxic) T lymphocytes, CD4/CD8 ratio being 0.14.

Findings led to diagnosis of Langerhans cell histiocytosis, affecting oral mucosa and periodontal tissues and infiltrating bone marrow, liver, spleen and skin.

Treatment according to Histiocyte Society protocol for severe progressive LCH was commenced, including 5 cycles of vinblastine and etoposide and continuous use of purinethol and pronison. After first cycle of chemotherapy bone marrow, liver and spleen showed remission, except for parietal bone scan which was still showing active process. Oral findings still showed progressive alveolar bone loss. No treatment was undertaken for oral lesions, except for microbial control with 0.2% chlohexidine rinse for home use. Chemotherapy was well tolerated and general status improved. Presently he is in remission, with good physical and mental development. Oral lesions are still present. Recent radiograph shows alveolar bone lysis, causing exposure of permanent teeth with undeveloped roots (Fig. 2).

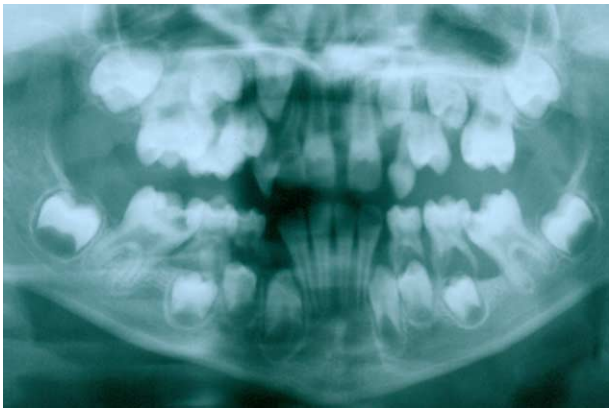

**Figure 2** On panoramic radiograph horizontal alveolar bone loss with premature ''eruption'' of permanent dentition could be seen. Roots of ''pseudoerupted'' permanent teeth are undeveloped.

## Discussion

Histiocytic disorders are rare and often unsuspected, thus it is rather uncommon for a dentist to be called upon to evaluate a child with severe periodontal destructive process which leads to distressingly premature eruption of permanent dentition. Furthermore, LCH could manifest itself with multiple presentations therefore leading often to an incorrect diagnosis.

Hernandez Juyol et al.[1] reported a case of fourteen month old boy who developed lytic lesions in the jaw which led to loosening of temporary molars. Minguez et al.[5] described 10 children with oral manifestations of LCH. Oral manifestations were the first sign of more generalized disease in 50% of cases, presenting as tooth mobility and loss, gingival bleeding and ulcerations. In some patients nonspecific pain, candidiasis, and orofacial swelling, as well as osteolytic areas on X-ray finding were noticed. Shaw and Glenwright[8] found facial swelling, gingival necrosis and loss of alveolar bone together with juvenile periodontitis or localized marginal periodontitis. Artzi et al.[9] reported a case of an adult presented with painless left submandibular mass which progressively increased. The patient had edematous and inflamed mandibular attached gingiva together with erosions and ulcerations covered with pseudomembranae which could be peeled off. Cranin and Rockman[10] described three cases of oral LCH presenting with loose molars, periodontal disease and precocious eruption of the primary dentition with gingival bleeding. Bottomley et al.[11] described a case of a patient with LCH with only oral soft tissues involvement but without bony involvement. Cleveland et al.[12] described three patients with primary manifestation of LCH in the oral cavity without bone involvement as multiple ulcerations on the hard palate in one patient, leukoplakia of the mandibular vestibule in the second patient and

yellowish-nodular lesions of the maxillary gingiva and mucobuccal folds in the third patient.

Our patient had pronounced ostelysis of jaw bones visible on panoramic radiograph, as well as skull lesions revealed by 99mTc MDP bone scan. Jaw bones lesions are usually limited to mandible, and radiographically resemble lesions seen in aggressive periodontitis[4]. However, besides mandibular lesions, our patient also had maxillary lesions, causing pseudoeruption of permanent dentition.

Throughout literature[7,13] it has been reported that localized LCH tends to heal spontaneously, bringing interventional treatment at second plan. On the contrary and unfortunately, our case shows that even localized LCH does not necessarily tend to heal spontaneously, moreover it can progress to systemic disease. This finding has also been stated by Putters et al.[7]—''It is questionable if waiting for spontaneous healing is eligible in most cases''. Furthermore, we have to underline that local treatment of the localized LCH might not be sufficient as suggested by Putters et al.[7] and that in every case, multidisciplinary approach should be requested in terms of trying to exclude systemic LCH disease, as also Nakamura et al.[14] reported. Even, if our patient was treated locally, the systemic LCH would have developed. In our patients systemic LCH developed after 1.5 year, therefore frequent and continuous reviews should be addressed in every patient with localized LCH. At the end we might speculate that even systemic LCH was present but at the time not manifesting itself in visible clinical signs. We have to underline that contrary to the opinion of Hicks and Flaitz.[13] that every resident in-training easily recognizes LCH, our case shows that this is not the case.

It should be emphasized that the extension of LCH lesions on the periodontal tissue are more widespread when compared to the ones seen in marginal periodontitis. Differential diagnosis might include: dental or periodontal abscess, acute necrotizing ulcerative gingivitis, primary herpetic gingivostomatitis, recurrent aphthous ulcerations, traumatic ulcerative granuloma, granulomatous diseases (sarcoidosis, tuberculosis, etc), benign and malignant tumors of the oral cavity (lymphoma, ameloblastoma, etc.) as well as oral manifestations of malignant blood diseases (leukemia, multiple myeloma, etc.).

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