Case Report

Langerhans cell histiocytosis: A diagnostic enigma in the oral cavity

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Abstract

Langerhans cell histiocytosis (LCH) is a rare reactive and proliferative disease of histiocytes. The disease occurs predominantly in children and rarely in adults. This disease of unknown etiology exhibits extreme clinical heterogeneity. Even though LCH manifests initially in the oral cavity in most of the cases, owing to the relative rarity of the condition, it remains a disease in which the diagnosis is often delayed, missed or misdiagnosed. This is a case of LCH in a child which presented with swelling in the mandibular region.

Keywords: Eosinophils, histiocytes, Langerhans cell histiocytosis, Langerhans cells

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease characterized by proliferation, infiltration and accumulation of a specific histiocyte known as the Langerhans cell. The incidence of LCH is reported to be 3–5 per million in children but rare in adults. It mostly occurs with a male predilection.[1] The etiology of LCH is unascertained, with various theories suggesting roles for environmental, infectious, immunologic and genetic causes and even as a neoplastic process.[2] LCH is characterized by its highly variable clinical presentation ranging from isolated skin and bone lesions to multisystem manifestations which may be life-threatening.[3] LCH may affect the oral and maxillofacial region with reported symptoms of gingivitis, periodontitis, tooth rotation or premature tooth loss and malocclusion, often with an ill-defined unilocular radiolucency.[4]

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This report describes a case of LCH which had presented with oral manifestations without any systemic signs or symptoms and hence emphasizes the importance of a dentist in the early diagnosis.

CASE REPORT

A 10-year-old male child reported to the Department of Pedodontics and Preventive Dentistry with the chief complaint of swelling in the lower left region of the jaw for 2 weeks. The mother of the patient gave a history that he had no pain or other difficulties. Craniofacial trauma, medication use, environmental allergies or previous surgeries were not reported. His medical history was not significant.

Approximately 2 years ago, the patient had a history of painless, firm, nontender, well-defined swelling on the

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right side of the mandible with a duration of 4 weeks. Intraoral examination revealed poor oral hygiene with calculus deposition. 75 was grade II mobile with gingival recession. Bleeding on probing was noted in relation to 55, 16, 75, 36, 85 and 46. Complete blood routine examination was normal. Peripheral smear showed mild hypochromia and eosinophilia. Periodontal therapy was done and oral hygiene instructions were given. On review after 1 week, there was no improvement for fragile gingiva and bleeding on probing. Pus discharge and ulceration were present in 85.46 regions. Incisional biopsy of the site was done and on histopathologic examination, diagnosis of ulcerative gingivitis was given. The patient was kept on follow-up and advised further periodontal treatment and symptomatic care.

On physical examination, the patient was moderately built, moderately nourished and well oriented to the surrounding. The child was calm and cooperative for clinical examination.

On extraoral examination, mild facial asymmetry with a diffuse and firm swelling measuring 4 cm × 3 cm in the left mandibular region was noted [Figure 1]. The swelling was nontender and the temperature of the skin over the swelling was normal. Left submandibular lymph nodes were palpable. Oral hygiene status was poor with increased accumulation of calculus and halitosis. Mandibular left premolars and right first premolar exhibited grade II mobility and the rest of the teeth were grade I mobile. Gingiva was fragile and exhibited ulceration in the 34–36 region.

Orthopantomogram revealed a mixed radiolucent-radio-opaque lesion in relation to the left side inferior border of the mandible in the left second premolar and first molar region. Mandibular second premolar exhibited floating tooth appearance with marked alveolar bone loss, but with buccal cortical plate expansion [Figure 2]. Occlusal radiograph showed periosteal reaction in the mandibular molar region on the left side [Figure 3]. Based on the clinical examination and radiographic findings, a provisional diagnosis of Garre's osteomyelitis was made. Differential diagnosis included aggressive periodontitis and fibroosseous lesions.

Periodontal therapy was initiated, focusing on aggressive periodontitis among other differential diagnoses. Deep scaling was done. Metrogyl DG for topical application was prescribed. Oral hygiene instructions along with saline rinse were advised. When the patient was reviewed after 1 week, no significant improvement in periodontal conditions of the remaining teeth or the severity of oral lesions was achieved. Consequently, eosinophilic granuloma was strongly suspected. Following extraction of the tooth with severe mobility, the socket was curetted [Figure 4] and the specimen was sent for histopathological examination.

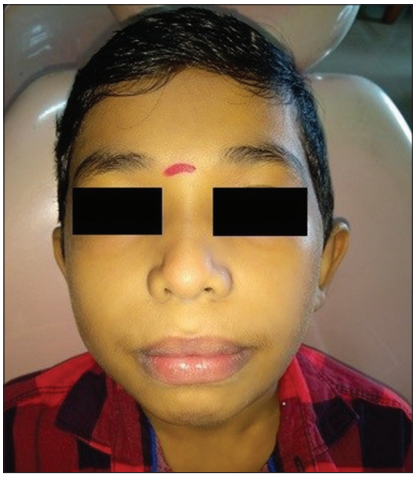

Figure 1: Extraoral photograph of the patient

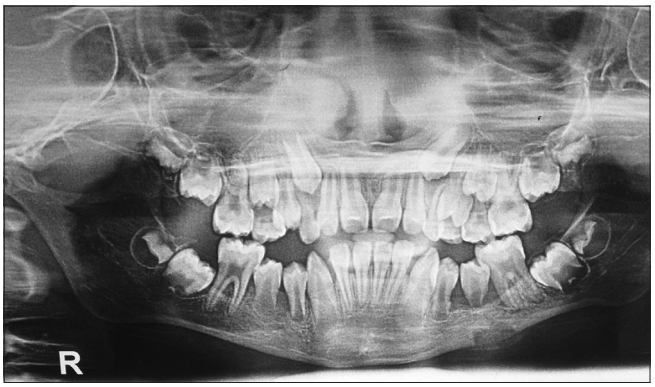

Figure 2: Orthopantomogram revealed a mixed radiolucent radioopaque lesion in relation to the inferior border in the region of 35, 36 and marked alveolar bone loss showing floating teeth in 35 region

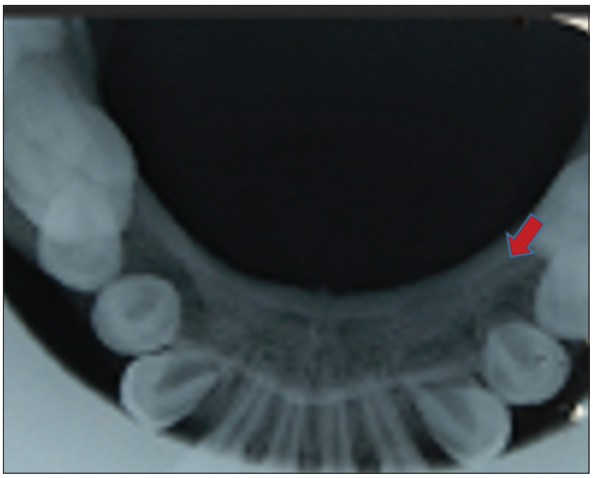

Figure 3: Mandibular true occlusal showing periosteal reaction in 35, 36 region

On histologic examination, H&E stained sections revealed an admixture of cell population comprising of histiocytes containing abundant, pale eosinophilic cytoplasm and eosinophils with bilobed, spectacle-shaped nuclei. Cells with relatively pale cytoplasm containing irregular and elongated nuclei with indentations imparting coffee-bean-shaped appearance were also seen which are presumably Langerhans cells. This group of cells comprised a majority of the cell population along with plasma cells and lymphocytes. Occasionally, multinucleated cells were found. Numerous blood vessels lined by plump endothelial cells and extravasated RBCs were also noted. The intervening delicate connective tissue showed haphazardly arranged collagen fibers with few fibroblasts and fibrocytes [Figure 5a and b].

Immunohistochemical analysis showed Langerhans cells staining positive for CD 68 [Figure 6a], S-100 [Figure 6b] and CD1a [Figure 6c] (Monoclonal, Biogenix) while being negative for pan CK and Vimentin (Monoclonal, Biogenix). With the above findings, a diagnosis of LCH was made.

The patient was sent for medical consultation for further systemic evaluation. Multiplanar MR imaging of the head was performed using a dedicated head coil, without contrast. It revealed a lytic area measuring 7 mm × 8 mm in the left parietal bone with a beveled edge which appeared hyperintense in T2 and isointense in T1. Another small lytic area was noted in the frontal bone. The lytic area with erosions was noted in the left mastoid bone extending into the squamous part of the left temporal bone. MRI features were suggestive of LCH. Chest radiograph was normal and USG abdomen showed no secondaries in the liver, but left renal calculus was present. The patient was examined for other lytic lesions in the skeleton apart from the skull but none was found. The diagnosis of LCH with cranial involvement (multifocal type) was confirmed.

After tumor board discussion, a treatment plan of systemic steroids and chemotherapy was suggested. The patient was referred to the Regional Cancer Center for further treatment.

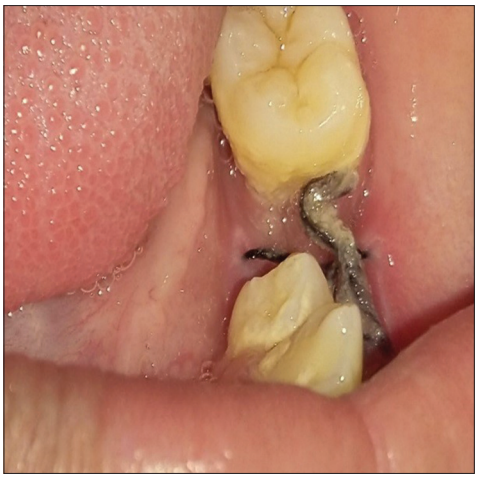

Figure 4: Healing extraction socket

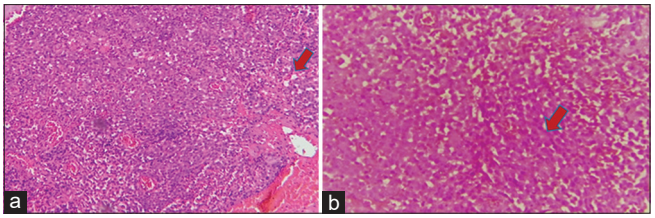

Figure 5: (a) Photomicrograph shows aggregates of histiocytes along with lymphocytes and eosinophils (H&E, ×100). (b) High-power view shows aggregates of histiocytes with indistinct cell borders and pale eosinophilic cytoplasm (H&E, ×400)

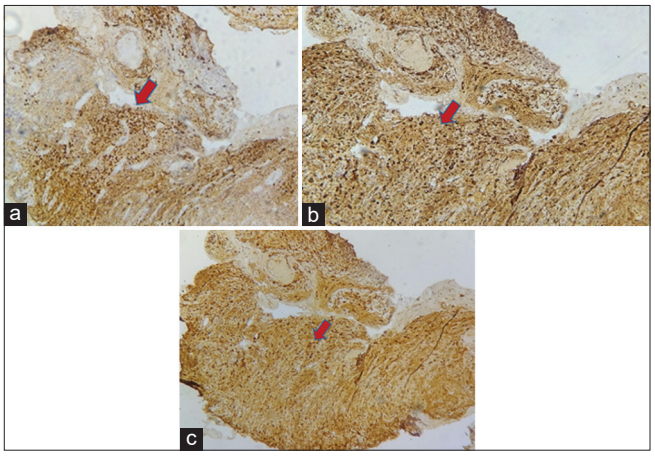

Figure 6: (a) The histiocytic cells showing positivity for CD 68 protein (IHC stain, ×100). (b) S-100 immunopositivity in nucleus and cytoplasm of Langerhans (IHC, ×100). (c) Uniform membrane staining of Langerhans cells with CD1a (IHC, ×100)

DISCUSSION

LCH is a clonal disease of myeloid dendritic cells that can affect all age groups but mainly children aged 1–4 years.[5] By virtue of being a rare disease, it is at great risk of being underdiagnosed or misdiagnosed. It is, therefore, of utmost importance that LCH is kept in mind when dealing with unclear osteolytic bone lesions.

Historically, LCH was called "Histiocytosis X"[6] which was classified into three categories based on the age and clinical presentation. These variants include (1) acute disseminated form with multiple system involvement often occurring mainly in infants known as Letterer–Siwe disease. (2) Chronic localized form with solitary or multiple skeletal lesions and occasionally extraskeletal involvement mainly seen in adults known as eosinophilic

granuloma. (3) Chronic disseminated form with osseous lesions which are frequently multiple and with extraskeletal lesions known as Hand–Schuller–Christian disease. Hashimoto–Pritzker syndrome is a congenital form of LCH presenting with deep subcutaneous skin lesions. Recently, a revised classification of histiocytoses was published by the Histiocyte Society in which LCH is subclassified according to the site of manifestation and organ involvement as single system LCH, lung LCH and multisystem LCH with or without risk organ involvement (risk organs: liver, spleen and bone marrow).[4] Bone followed by the skin, lymph nodes and lung are mostly involved in single-system LCH.[7] Skeletal lesions of LCH often affect the skull, long bones, pelvis, ribs, vertebra, facial bones and jaws, particularly the posterior regions of the mandible.[8]

It has been proposed that loss of heterozygosity on chromosomes 1, 4, 6, 7, 9,16, 17 and 22, chromosomal instability and elevated expression of oncogene products, such as p53, H-ras and c-myc, causing disrupted cell cycle regulation are considered to cause LCH.[9] Mutations in the MAPK pathway have been identified in approximately 75% of patients with LCH. In addition, immunohistochemical studies were able to identify the expression of the common BRAFV600E mutation in CD 207+.[10]

Radiologically, LCH presents as localized, punched-out radiolucency with no calcification, sclerosis or reactions at the borders. There may be severe alveolar bone resorption producing the appearance of teeth "floating in space"[2] as in this case.

The histologic picture reveals histiocytes with abundant eosinophilic cytoplasm and lobulated or coffee bean-like nucleus containing delicate chromatin and inconspicuous nucleoli admixed with variable number of eosinophils, lymphocytes, neutrophils, plasma cells and multinucleated giant cells.[11] The characteristic immunophenotype of LCH includes expression of CD1a, S100 protein and langerin (CD207) in Langerhans cells. On electron microscopy, elongated, zipper-like cytoplasmic Birbeck granules are observed.[7] Histological examination in the present case revealed large polygonal cells in the subepithelium indicating a poorly differentiated tumor. However, close scrutiny showed nuclear grooves bringing histiocytic disorder in the differentials. A dense nonspecific inflammatory infiltrate also hindered the recognition of these tumor cells. According to The Working Group of the Histiocyte Society, a definitive LCH diagnosis can be set when, in addition to these light microscopy features, Birbeck granules can be detected in lesional cells by electron microscopy and/or a positive staining for CD1a antigen can be obtained.[12] Langerin (CD207) is a relatively new immunohistochemical marker that may serve as a surrogate indicator for the presence of Birbeck granules in LCH histiocytes.[11,13] In this case, S-100, CD-68 and CD1a immunostaining were positive which were confirmatory for LCH.

Differential diagnoses of LCH comprise other cutaneous histiocytoses such as xanthogranulomas, normolipemic granulomas, histiocytomas or hemophagocytic lymphohistiocytosis. Other differential diagnoses were multiple myeloma and metastatic carcinoma; they were also ruled out as there were no general systemic manifestations. The histopathology is similar in all LCH variants except in acute disseminated form as they also demonstrate the acute form of lymphomas.[4] When encountered in the oral cavity, differential diagnosis of LCH poses a significant challenge for the dental professionals, as several clinical features of the disease resemble more common conditions including periodontal disease, malignancies and granulomatous or ulcerative lesions.[13]

Accordingly, clinical and radiological findings of the present case entailed a primary diagnosis of ulcerative gingivitis. Re-evaluation of the patient and an excisional biopsy for histopathological examination along with immunohistochemistry helped to reach the correct diagnosis.

Surgical treatment has been shown to be very effective in the treatment of localized oral manifestations of LCH and is usually regarded as being sufficient as a sole treatment, sometimes combined with steroid injections. If surgical removal of the affected area is not possible or if LCH recurs in the same location, radiation therapy may serve as an alternative or second-line treatment. In severe cases with organ dysfunction or systemic LCH manifestations, chemotherapy significantly improves the outcome.[4] In addition to traditional therapeutic combinations, monoclonal CD-1a-antibody-therapy and gene transfer into hemopoietic progenitor cells represent new therapeutic strategies.[14]

According to the prognostic criteria for LCH, age - <2 years, number of sites involved - multisystem disease and organ dysfunction results in poor prognosis.[4]

CONCLUSION

Although LCH may be self-limiting or locally recurrent, high-risk cases with systemic involvement can have fatal outcomes. The symptoms of LCH may occur first in the

oral cavity before other symptoms in the body. Hence, a thorough examination along with establishing and ruling out differential diagnoses is relevant in its early detection. The diagnosis of LCH is reached by evaluating clinical and radiographic findings and confirmed by histopathological and immunohistochemical studies. Pediatric dentists as well as general practitioners play an important role in educating the parents about the disease, the treatment and the possible outcome and also in referring the patients to specialty centers for appropriate treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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