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LANGERHANS CELL HISTIOCYTOSIS PRESENTING AS AN ORAL LESION: A CASE REPORT AND LITERATURE REVIEW

Dental Science

***Dr. Smita Shrishail Birajdar**	Department of Oral Pathology, Vishnu dental college, Bhimavaram *Corresponding Author
Dr. Radhika M.B	Department of Oral Pathology, Krishnadevaraya college of dental sciences, Bangalore
Dr. Soumya Makarla	Department of Oral Pathology, Krishnadevaraya College of Dental Sciences, Bangalore
Dr. Shrinath	Department of Oral Surgery, Krishnadevaraya college of dental sciences, Bangalore
Dr. Paremala K	Department of Oral Pathology, Krishnadevaraya college of dental sciences, Bangalore
Dr. Sudhakara M	Department of Oral Pathology, Krishnadevaraya college of dental sciences, Bangalore

ABSTRACT

Langerhans cell histiocytosis (LCH), also formerly known as histiocytosis X and currently regarded as a myeloid neoplasm, is a disease characterized by proliferation of cells exhibiting phenotypic characteristics of Langerhans cells. LCH includes a wide range of clinical presentations from a single system involvement such as the skin or bone to a multifocal disease involving liver, lungs, bone marrow and CNS. Although the pathogenesis of LCH remains enigmatic, the disease seems to be associated with abnormalities in the biology of Langerhans cells and macrophage infiltrates in the lesions.

Here we present a case of LCH of a 4- year- old male child who presented with a swelling of the body of mandible on the left side.

KEYWORDS

Langerhans cell histiocytosis (LCH), Langerhans cells (LC), Histiocytosis X

INTRODUCTION

The histiocytoses comprise a diverse group of proliferative disorders characterized by the accumulation of histiocytes and their infiltration along with other immune effector cells. The generic term "histiocyte" refers to several types of cells including: monocytes /macrophages, dermal /interstitial dendritic cells and Langerhans cells (LC). [1]

LCs in Langerhans cell histiocytosis (LCH) originate in the bone marrow and are derived from CD 34 positive stem cells rather than from epidermal Langerhans cells. They express certain number of surface phenotypic markers, among which the most important are the major histocompatibility complex (MHC) class II molecules and the antigen CD1a.[2] LCs like other dendritic cells, have a critical role in the immune system secondary to either immune dysregulation or following exposure to a yet undetermined stimulus.[3] Currently, the term *Langerhans cell histiocytosis (LCH)* is used to include a spectrum of disorders previously designated as eosinophilic granuloma, histiocytosis X, Hand-Schuller-Christian disease, and Letterer-Siwe disease. [4]

LCH is a monoclonal disorder caused due to abnormal proliferation of LCs and their aberrant migration to abnormal locations when compared with the normal sites of occurrence which may play a role in the pathogenesis. [5] It is a unifocal or multifocal disorder with highly variable biological behavior and clinical severity. [6] LCH is generally a sporadic disease that occurs predominantly, but not exclusively in children. The occurrence of LCH in the oral cavity is rare; however, there are reports of LCH in oral mucosa and the jaws. [7] The cornerstone of diagnosis in LCH includes identification of the characteristic clinical features, but also corroboration of histopathologic and immunohistochemical results. [8]

Here we present a rare case of LCH in a 4-year -old male patient who had come to the hospital with a chief complaint of painless swelling of the mandible since 3 months. The main intention of this case report is to emphasize the critical role of dentist in recognizing this rare disorder, which can present primarily as an oral lesion and the necessity of subjecting such cases to a thorough systemic evaluation and early treatment.

CASE REPORT

A 4 year old Indian boy reported to the outpatient department of Krishnadevaraya College of Dental Sciences, Bangalore with a complaint of a painless swelling in the left side of the mandible since 3 months.

Extra- oral examination revealed a mild asymmetry with a solitary, diffuse swelling measuring about 4.0 cm x 3.0 cm extending anteroposteriorly 2 cm behind the left corner of the mouth till the angle of the mandible and superoinferiorly from the ala tragus line to the lower border of the mandible . The skin over the swelling appeared normal with no secondary changes. (Fig1:)

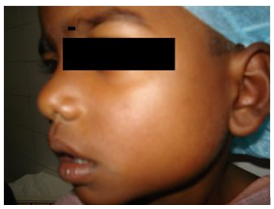


Fig 1: Extra oral diffuse mandibular swelling involving angle of the mandible

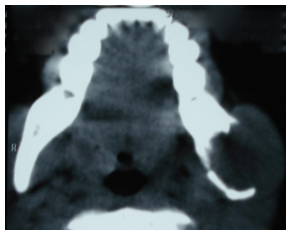
Intra-oral examination revealed a diffuse swelling measuring about 3.0 X 2.0 cm extending from distal aspect of deciduous first molar (74) to the retromolar region obliterating the buccal vestibule. Overlying mucosa was intact with no change in color or discharge (Fig 2:).

Fig 2: Intra oral diffuse swelling involving retro molar region with obliteration of vestibule

The general and head and neck examination was non contributory, with absence of cervical lymphadenopathy. No similar familial history revealed. The patient was advised for radiographic examination.

The frontal view radiograph showed multilocular radiolucency with buccal and lingual cortical bone erosion. A Computed Tomographic (CT) scan revealed a lytic lesion involving the left side of the mandible extending to involve mandibular first deciduous molar up to the ramus

area (Fig 3:). By correlating the clinical and radiographic features, a provisional diagnosis of odontogenic cyst was given.



IFig 3: C T Scan showing multilocular radiolucency with buccal and lingual cortical bone erosion

Fine needle aspiration cytology (FNAC) was performed which showed numerous large tumor Langerhans cells with an abundant pale cytoplasm containing round to oval eccentric nuclei. Few cells showed moderate to large amount of cytoplasm exhibiting vacuoles and these cells were admixed with abundant numbers of eosinophils and giant cells in the background of RBCs (Fig 4:).

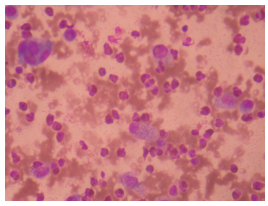


Fig 4: The peripheral blood smear showing numerous eosinophils admixed with blast cells

Other laboratory values were within the normal limits. The patient was explained regarding the treatment and informed consent from the parents was obtained. The lesion was curetted thoroughly under general anesthesia. The surgical site was cleaned with povidone iodine solution and closed with sutures. The lesional tissue was sent for histopathological examination

The gross specimen consisted of three large and several small soft tissues. All the soft-tissue bits were white to dark brown in color and firm in consistency. The largest tissue measured 1.3 cm x 0.3 cm x 0.6 cm while, the smaller soft-tissues collectively measured 1.0 cm x 0.3 cm x 0.6 cm in size.

On microscopic examination, the lesional tissue showed diffuse infiltration of mononuclear cells resembling histiocytes with indistinct cytoplasmic borders. These cells showed pale staining cytoplasm with round nucleus which appeared folded or grooved resembling a coffee bean along with prominent nucleoli. Numerous eosinophils with intensely eosinophilic granular cytoplasm with bilobed nucleus along with neutrophils and multinucleated giant cells and areas of hemorrhage were evident (Fig 5and 6:).

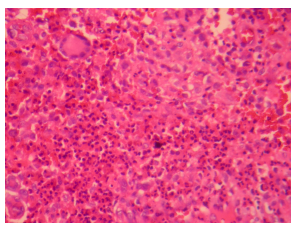


Fig 5: H & E section in 20X showing mononuclear histiocytic cells along with eosinophils and giant cells

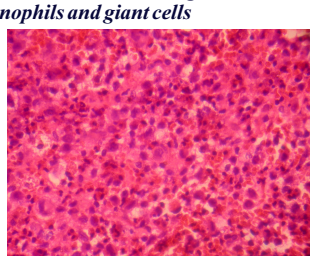


Fig 6: H & E section in 20X showing sheets of mononuclear histiocytic cells with coffee bean nuclei along with numerous eosinophils

Immunohistochemical (IHC) staining, for the confirmation of LCs, showed strongly positive CD1a cells. Based on the histopathology and IHC it was diagnosed as LCH (Figure 7).The patient has been under regular follow-up for 7 years and remained free of recurrence or new lesions.

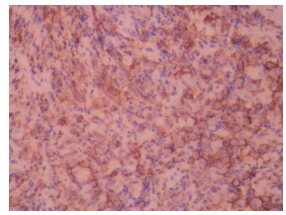


Fig 7: Immunohistochemical staining with CD1a showing cell membrane positivity

DISCUSSION

The histiocytoses comprise a diverse group of proliferative disorders characterized by the accumulation of histiocytes and their infiltration along with other immune effector cells. The generic term "histiocyte" refers to several types of cells including: monocytes ⁄ macrophages, dermal ⁄interstitial dendritic cells and Langerhans cells (LC). [1]

The Histiocyte Society has proposed the reclassification of histiocytosis based upon the predominant cell type within the infiltrate. The classification system includes four divisions: dendritic disorders (including LCH), macrophage-related disorders, malignant histiocytic disorders and dendritic cell or macrophage-related histiocytic sarcoma. [7]

Langerhans cell histiocytosis (LCH), a rare disease, is currently regarded as a myeloid neoplasm, with remarkably broad clinical spectrum, ranging from isolated skin or bone lesions to a disseminated disease that can involve nearly any organ [9] which may be the result of an uncontrolled and abnormal proliferation of LCs. Owing to the relative rarity of the condition, it remains a disease in which the diagnosis is often delayed or missed and in which many questions remain unanswered, ranging from etiology and pathogenesis to therapy. [10] The etiopathogenesis of LCH has not been fully determined, and the occurrence of spontaneous remission and the benign histopathological appearance of the lesions in LCH suggest a reactive clonal disorder rather than a malignant process, at least in some cases. [11] Molecular genetic studies have demonstrated that all forms of LCH are clonal in nature. [12] However, the presence of clonal accumulations, chromosomal instability and significant telomere shortening of the LCs compared with LCs from other inflammatory lesions, the presence of cell-cycle dysregulation within lesions and recently BRAF c.1799T>A (p.Val600Glu) mutation in LCH are strong evidence of the neoplastic nature of the disease. [9]

The current clinical classification of LCH describes a broad spectrum ranging from localized single-system involvement to disseminated multisystem disease. The severity of LCH is usually age-related. Extensive multisystem variants with a poor prognosis and mortality rate up to 50% have been primarily described in early childhood, whereas multifocal single-system disease is often diagnosed in children aged up to 5 years. As well, unifocal bone restricted disease is primarily a disease of older children. [9]

It is generally regarded as a sporadic disease that occurs predominantly in the pediatric population showing male predilection, with an estimated annual incidence of 4-5 per million. It can occur at any age; children below 15 years of age have a higher incidence rate of 8.9 persons per million and 1–2 persons per million in neonates below 28 days of age and dropping to 1–2 cases per million in adults. [9] Several large retrospective studies consisting of neonates and children under the age of 4 years have shown that 51% to 71% of children with LCH present with multiorgan disease. [1] More than two-thirds of cases have single system disease with bones and skin as the most commonly involved sites although lymph node, lung, and other sites may be involved. Involvement of head and neck region with LCH has been observed in 82% of cases. [13] Greenberger et al found that children younger than 2 years of age and with multiorgan involvement had a higher mortality rate. Thus, comprehensive evaluation of all children is mandatory. [14] In this case report only mandibular jaw bone i.e., single system involvement has been observed which is uncommon in young child.

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 radiographic examination were noticed which can be easily mistaken for other common dental disorders.[15] In our case, an intraosseous painless swelling was noted.

Radiographs demonstrate a "punched out" radiolucency with a sharply defined margin. Computed tomography studies (CT) are more sensitive in demonstrating the extent and progress of the disease. The CT image generally has indistinct bone margins in association with a homogeneous soft tissue mass. [16] Here in our case the CT scan showed both buccal and lingual cortical bone destruction with irregular lytic lesions.

It is essential to note that the clinical and radiographic presentation of LCH could mimic an acute or chronic periodontal or periapical lesion, radicular cysts, osteomyelitis and malignancies. The lesions often appear as sharply punched-out radiolucent images, and the teeth appear to be "floating" when extensive alveolar involvement.[17]

As LCH lacks pathognomonic clinical or radiographic characteristics, a definitive diagnosis should be based on the histopathological and immunohistochemical study of lesional biopsy specimens. Histologically, LCH is characterized by diffuse infiltration of large, pale- staining mononuclear cells that resembles histiocytes which have indistinct cytoplasmic border and round or indented vesicular nuclei. Varying numbers of eosinophils are dispersed among the histiocyte-like cells. Plasma cells, lymphocytes and multinucleated giant cells are often seen. [17]

The diagnosis can be confirmed by positive immunostaining for CD1a, S-100 protein, lysozyme, langerin, vimentin, CD4, CD 11c, placental alkaline phosphatase, CD68, and the presence of Birbeck granules (elongated, zipperlike cytoplasmic structures measuring 200 to 400 nm) at the ultrastructural level. [18]

Immunostaining positivity is characteristically observed for CD1a, langerin (CD207) and S-100 protein. [9] S100 though sensitive has a very low specificity. Recently used new antibody, langerin (Cd207), has been shown to be more specific and sensitive which reacts with a type II Ca^{2+} dependent lectin associated with Birbeck granules.[19]

Because monoclonal proliferation of CD1-positive histiocytes has been shown in all forms of LCH disease, the narrow specificity of the antibody and the ease of the immune staining process render immunostaining for CD1a useful as a routine procedure for diagnostic confirmation of LCH. [20] In our case CD1a immunostaining was positive which showed cell membrane positivity for Langerhans cells and hence confirmatory for LCH.

The treatment of LCH is dependent on lesion size, the degree of tissue involvement and whether it is unifocal or multifocal. Therapy includes surgery, radiation, and chemotherapy, either individually or in combination. [21]

The first step in the treatment of LCH should be to determine the number of organ systems involved.Then the patients who have single-system disease should be subcategorized based on the number of sites involved. The presence or absence of organ dysfunction is a subcategory for patients who have multi-organ disease. [1]

Curettage is generally sufficient for patients with localized bone lesions. [13] However, it is also possible to employ intralesional steroids or low-dose radiation. Treatment of multiorgan disease is controversial with some advocating high-dose prednisone as the first-line therapy, whereas others suggest use of single-agent chemotherapy. [22] Recurrence rates depend on the treatment method and location of the lesion and are reported to range from 1.6% to 25% and patients should be closely followed up for a long period of time. [23]

The prognosis of patients with bone involvement is extremely favourable with an overall complete and sustained remission rate of approximately 80 - 95%. As the disease can be unpredictable, it is mandatory that all cases have to be subjected to a careful follow-up for identifying signs of recurrence and dissemination. Progression of an initial solitary lesion into a disseminated condition has been reported within 6 months in patients below 5 years of age in the literature. Hence the potential for unifocal disease to become multifocal should be appreciated. [13] The present case was treated with curettage and follow up done till date. The patient is free of post – operative complications and no recurrence is reported in the 8 year follow up which is in accordance with the literature showing excellent prognosis of single bone involvement.

Despite adequate treatment, survivors of LCH in childhood may have long-term sequelae, some of which may not become apparent until many years later. One retrospective study of patients with a history of multi-organ system LCH found that 75% had detectable long-term sequelae with hypothalamic-pituitary dysfunction (50%), cognitive dysfunction (20%), and cerebellar involvement (17.5%). Other sequelae may be multifactorial, such as growth retardation and second malignancies, including solid tumors and hematopoietic malignancies. Not only patients with multisystem disease are at risk for long term complications, but also approximately 25% of patients with single-system disease may experience permanent sequelae. [24] Hence the utmost beneficial factors towards patient care are early detection of the disease and appropriate referral and follow-up measures.

CONCLUSION

In conclusion, the frequent occurrence of oral lesions in LCH emphasizes the need for an interdisciplinary approach to the diagnosis, as the oral lesions can be the initial feature of the disease. Prognosis remains poor despite utilizing all chemotherapy options. Novel therapeutics offer new potentials by opening new fronts in combating LCH. This is only possible by further research in the quest for better understanding of this disease.

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No conflict of interest.

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