Langerhans Cell Histiocytosis – A Review and Case Report

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ABSTRACT
Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X is a selectively rare disease with an incidence of 2-5 cases per million. It refers to group of conditions characterized by uncontrolled stimulation and proliferation of normal antigen-processing bone marrow derived cell- langerhans cells. Langerhans cells histiocytosis mainly affects the skull, vertebrae, ribs, maxilla and mandible in children and the long bones of adults. Symptoms range from none to pain, swelling and tenderness over the site of lesion, gingival enlargement, oral ulcers, and mobility of teeth. This disease presents oral manifestations which can be expression of the systemic condition, hence diagnosing such lesion becomes difficult for oral physicians, and LCH is confirmed by histological, immune histochemical staining. These lesions are commonly seen in childhood; we report a case of 15 years old male child, who presented with swelling of gums, mobility of almost all teeth since 6 months. On the basis of histological and immune histochemical features (tumor cells are positive for CD 1a and S100 protein); a diagnosis of langerhans cell histiocytosis was made.

Key words: Histiocytosis X, langerhans cell histiocytosis,

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INTRODUCTION
In 1953, Lichtenstein observed cytoplasmic bodies, known as X bodies, within histiocytes from tissues of patients suffering from that were previously considered distinct clinical disorders: Letterer- Siwe disease, Hand-Schuller-Christian disease, Eosinophilic granuloma .As a result of their common underlying histopathology, Lichtenstein grouped these diseases together under the name of histiocytosis X. The letter “X” denotes unknown etiology. In 1973 term Langerhans Cell Histiocytosis was adopted because it is characterized by a proliferation, infiltration and accumulation of a specific histiocyte, namely, the pathological Langerhans cell, which is considered to be a special type of dendritic mononuclear cell (derived from bone marrow), within a variety of tissues and organs . Letterer-Siwe Syndrome-Acute disseminated form of disease Characterized by cutaneous lesion, hepatomegalias, splenomegalias, ganglionic hypertrophies. Bone lesions occur in skull, long bones and mandible. Lesions in mandible show a definite radiolucent image which may mimic both juvenile and severe periodontal disease.

Hand-Schuller-Christian disease- Chronic disseminated form of disease characterized by traid – exopthalmos, diabetes insipidus and osteolytic lesions in skull. Oral findings – increased gingival volume, bleeding, deep pockets, alveolar bone loss, tooth mobility, resembling periodontitis. Earliest sign usually manifest during childhood. Prognosis of this clinical varient is better than the Letterer- Siwe syndrome.

Eosinophilic granuloma- Chronic localized form characterized by single or multiple osseus lesions, affecting children or young adults. Prognosis is excellent and lesion may spontaneously recede within one or two years.

In 1973, Nezelof revealed histiocytes were actually Langerhans cells so the disease was renamed Langerhans cell histiocytosis, LCH is also named as Langerhans cell granulomatosis, Histiocytosis X, Hashimoto-Pritzker’s syndrome, Non lipidic reticuloendotheliosis type.

CASE REPORT
A 16 year old male patient reported to our department with history of swelling and bleeding of gums, difficulty in chewing, burning sensation and Generalized tooth
mobility. Nothing significant was reported in medical history by the patient and no history of trauma was given by the patient. On General physical examination all vital signs were within normal limits and patient was well nourished.

**Clinical Examination**
On intraoral examination, oral hygiene was poor, gingiva was red, fragile, hyperplastic, Interdental papilla was missing with respect to 31,41, Generalized tooth mobility, On palpation abscess was present, Pseudomembranous slough and halitosis was present. (Figure 1)

![Figure 1: Pre-operative photograph](image1)

On radiographic examination ill defined radiolucency was seen with respect to lower premolar region (Figure 2) and generalized bone loss was present. In Chest radiography no abnormality was detected.

![Figure 2: Radiograph](image2)

**Investigation**
Ultrasound test of the abdomen showed normal-sized spleen and liver; in CBC all values were in normal limits except serum alkaline phosphatase level, it was elevated. (Figure 3)

![Figure 3: Blood investigations](image3)

**Clinical Diagnosis**
Excisional biopsy was done under local anesthesia and sample was sent for histopathological examination. Histopathological reports revealed Langerhans cells (coffee bean shape nuclei) interspersed with eosinophils. On Immunohistochemical examination tumour cells were positive for CD1a and S100 protein. Based on above examinations, LCH was diagnosed and confirmed. (Figure 4)

![Figure 4: Histopathology report](image4)
DISCUSSION
Paul Langerhans (1868) was the first to describe langerhans cells, as dendritic shape cells located in squamous layer of epithelium. These are potent antigen-presenting cells plays a role in local defense mechanism in epithelium. These serve as sentinel of oral mucosa and inform the immune system not only about the entry of pathogen, but also about the tolerance to self-antigens and commensals microbes. Characteristic feature of this cell is presence of g-specific granules or birbeck granules (100nm to 1µm in size) first described by Birbeck et al in 1961. These granules are rod shaped and if terminal vesicle is present, they assume the classic tennis racket like appearance. Exact nature of these granules is no clear; however they have been associated with antigen trapping and presentation.

On the basis of electron microscopic appearance, these cells have been divided into two types –

Type 1: these are pyramidal in shape and are highly dendritic with an electrolucent cytoplasm. They have numerous Birbeck granules and are usually found in the suprabasal layers.

Type 2: these are spherical in shape and show fewer dendrites, more electron dense cytoplasm with fewer birbeck granules. They are usually located in basal layer.

Langerhans cell histiocytosis (LCH) mainly affects young children and is histologically characterized by the proliferation of CD1a+ Langerhans cells. Clinically, it is difficult to distinguish oral LCH lesions from chronic periodontitis, pre pubertal periodontitis, bone metastases, oral ulceration by HIV infection, lymphoma, vasculitis (Wegener granulomatosis).

In the present case, from the initial clinical signs, radiological and blood examination suggested none of the above-mentioned diseases. Radiological pattern of bone loss resembled juvenile periodontitis. Failure of the measures to eliminate inflammation completely at a later stage favors the diagnosis of periodontitis as a manifestation of systemic disease.

Several authors reported in histiocytosis oral signs are common early findings, and oral symptoms may antedate other form of the disease by as much as 10 years. So children who shows the features of prepubertal periodontitis, the differential diagnosis should always include Histiocytosis “X.”

The etiology and pathogenesis of LCH is still unknown, but there are two different school of thoughts: a disorder of immune system or a neoplastic process. The presence of aggregates of other immunologically active cells in lesions, the presence of thymic abnormalities, and a deficiency in the number of suppressor T lymphocytes and increased cytokines suggest an exuberant reaction of Langerhans cells to an unknown antigen or neoantigen. However, the monoclonal proliferation of Langerhans cells infers the neoplastic origin of the disease. Different organs and systems may be affected by LCH, particularly bone, most commonly the skull and maxillary bones. Soft tissue involvement may occur, whereby lymph nodes, the lungs, and mucous membranes are commonly affected.

It is a very exceptional disease, incidence ranges from 0.5 to 5.4 cases per million persons per year. For such patient, the confirmative diagnosis was based on the histological and immunohistochemical analysis of the biopsy specimens.

The “gold standard” for LCH has been Identification and detection of Birbeck granules by transmission electron microscopy, however this technique is rarely performed today. A wide variety of treatment plans has been used to treat LCH, including wide surgical excision with radiotherapy, chemotherapy, isolated radiotherapy, and the use of alkalinizing agents. In the present case, oral lesions were treated by topical steroids – clobetasol propionate – 0.05%, as used by Manfredi et al. Patient undergone regular professional oral prophylaxis to decrease mucosal and periodontal damage, and patient was referred to an oncologist, where he was under chemotherapy (methotrexate and vinblastine with prednisone)

CONCLUSION
Dentist should be able to diagnose properly the oral lesions, as oral manifestation of LCH may be the first sign of disease, therefore, make excisional biopsy and appropriate treatment together. As oral manifestation in LCH may be misdiagnosed as other dental disorders.

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