

Langerhans Cell Histiocytosis: A Case Report and Review

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Abstract: Langerhans' cell histiocytosis (LCH) (Histiocytosis X) is a rare disease of unknown cause characterized by oligoclonal proliferation of Langerhans cells. It occurs mostly in children and young adults and involves one or more body systems such as bone, hypothalamus, posterior pituitary gland, lymph nodes, liver or various soft tissues. 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. This case report would increase the awareness of pediatric dentists about the dental manifestations and multisystem involvement in LCH. Key Words: LCH, histiocytes, Punched out lesions of bones.

Case Report: 5 year old boy was brought to our hospital with chief complaint of loose teeth, gingival swelling left facial swelling and left ear discharge since 3 months. The problem had started with a feeling of all teeth becoming loose 3 months ago. The swelling of gums and left facial region started 3 weeks before followed by left ear discharge.

Physical examination:

Extra – oral: Diffuse, mild swelling on left lower third of face with overlying erythematous surface (Figure 1).

Intra – oral:

1. Localised ulceration of size 3×2cm with indistinct borders on alveolar ridge of 74, 75, 36 and 84, 85, 46 region.
2. Grade III mobility of 81, 82, 83 and 84.

Orthopantomogram:

1. Extensive lytic lesions with ill-defined, irregular margins involving the mandible extending from 46 region continuously till left coronoid notch and almost whole left ramus of mandible (Figure 2).
2. Floating teeth in air appearance of 71, 72, 73, 74, 36, 81, 82, 83, 84 and 46.

Lateral skull radiograph: Multiple punched out lesions of skull (Figure 4, 6).

Lateral view of mandible: Lytic lesions of body and ramus of mandible (Figure 3, 5).

I. Introduction

Considering oral signs and symptoms, a tentative diagnosis of Histiocytosis was made as the first diagnosis and the malignancies and immunological disorders as second possibilities. The child was referred to Regional Cancer Centre (RCC), Medical College Hospital for further needful. The child was evaluated at RCC and was found to have history of skin lesions since 1 year, Ear discharge, Abdominal distension and loss of appetite with resultant weight loss of 6 month duration. The complete blood count (CBC), Inflammatory markers (ESR and CRP) and Lab work up were within normal limits. The child was referred back to our hospital for biopsy from lesions in mandible. The child was posted for biopsy under GA under Dept of Oral and Maxillofacial Surgery. Two samples were taken, one from each site and was sent for histopathological examination. Histopathological diagnosis was Langerhan Cell Histiocytosis (Figure 7). Hence patient was referred back to RCC for further management. Currently the child is undergoing Chemotherapy with LCH protocol at RCC.

II. Discussion

Langerhans cell histiocytosis (LCH) is a group of idiopathic disorders characterized by the presence of cells with characteristics similar to bone marrow-derived Langerhans cells juxtaposed against a backdrop of hematopoietic cells, including T-cells, macrophages, and eosinophils. In 1868, Paul Langerhans discovered the epidermal dendritic cells that now bear his name. The ultrastructural hallmark of the Langerhans cell, the Birbeck granule, was described a century later. The term Langerhans cell histiocytosis is generally preferred to the older term, histiocytosis X. This newer name emphasizes the histogenesis of the condition by specifying the type of lesional cell and removes the connotation of the unknown ("X") because its cellular basis has now been clarified¹.

Although the epidermal Langerhans cell has been presumed to be the cell of origin in LCH, recent studies have called this belief into question. Specifically, a variety of other cellular populations have been identified that possess phenotypic characteristics similar to Langerhans cells, including expression of CD207 and Birbeck granules. Therefore, in addition to epidermal Langerhans cells, other potential cellular origins for LCH include dermal langerin⁺ dendritic cells, lymphoid tissue-resident langerin⁺ dendritic cells, and monocytes that can be induced by local environmental stimuli to acquire a Langerhans cell phenotype^{2,3}.

Notably, LCH cells have been found to express markers of both resting epidermal Langerhans cells (CD1a, intracellular major histocompatibility complex II [MHCII], Birbeck granules) and activated Langerhans cells (including CD54 and CD58). As a result, the pathologic cells of LCH have been hypothesized to represent Langerhans cells in a state of arrested maturation³. Taken together, these findings have led some to speculate that LCH is not a specific disease of epidermal Langerhans cells, but rather one of mononuclear phagocyte dysregulation³.

The working group of the Histiocyte Society⁴ has divided histiocytic disorders into 3 groups: (1) dendritic cell histiocytosis, (2) macrophage-related disorders, and (3) malignant histiocytosis. LCH belongs in group 1 and encompasses a number of diseases. On one end, the clinical spectrum includes an acute, fulminant, disseminated disease called Letterer-Siwe disease, and, on the other end, solitary or few, indolent and chronic lesions of bone or other organs called eosinophilic granulomas. The intermediate clinical form called Hand-Schüller-Christian disease is characterized by multifocal, chronic involvement and classically presents as the triad of diabetes insipidus, proptosis, and lytic bone lesions. A congenital, self-healing form called Hashimoto-Pritzker disease has also been described.

The pathogenesis of Langerhans cell histiocytosis (LCH) is unknown. It has been debated whether LCH is a reactive or neoplastic process. Arguments supporting the reactive nature of LCH include the occurrence of spontaneous remissions, the extensive elaboration of multiple cytokines by dendritic cells and T-cells (the so-called cytokine storm) in LCH lesions, and the good survival rate in patients without organ dysfunction^{5,6}. On the other hand, the infiltration of organs by a monoclonal population of aberrant cells, the possibility of lethal evolution, and the cancer-based modalities of successful treatment are all consistent with a neoplastic process^{7,8}. Of note, recent genomic studies demonstrate activating, somatic BRAF mutations in the majority of human specimens. These observations support the concept of LCH as a myeloid neoplasm⁹.

Langerhans cell histiocytosis (LCH) is a rare disease. The estimated annual incidence ranges from 0.5-5.4 cases per million persons per year. The prevalence of Langerhans cell histiocytosis (LCH) seems to be higher among whites than in persons of other races, but many cases have been reported in Asian population¹⁰. The frequency of Langerhans cell histiocytosis (LCH) is greater in males than in females, with a male-to-female ratio of 2:1 in accordance with our case. Langerhans cell histiocytosis (LCH) affects patients from the neonatal period to adulthood, although it appears to be more common in children aged 0-15 years with peak incidence from 2 to 4 years as in our case.

Signs of Langerhans cell histiocytosis (LCH) depend on the localization and the extent of the disease. The clinical spectrum is broad, and an individual case may differ markedly from the prototypes described. Chronic unifocal LCH (eosinophilic granuloma of bone) classically presents as a solitary calvarial lesion in young adults; other frequent sites of involvement include vertebra, rib, mandible, femur, ilium, and scapula. Lesions are usually asymptomatic, but bone pain and a soft tissue mass may occur¹¹.

The classic multifocal form of LCH (Hand-Schüller-Christian disease) includes diabetes insipidus, exophthalmos, and bony defects, particularly of the cranium and head and neck region including oral cavity¹². If the underlying maxilla or mandible is destroyed in the course of disease, it manifests as gingival hyperplasia or ulceration. Bone lesions affect the skull and the mandible more than the maxilla. It is characterized by multiple punched out lesions in the skull and radiolucency mainly occurring in the central aspect of the mandible or maxilla. In alveolar lesions the lamina dura and surrounding bone along with the periodontium is destroyed which results in floating teeth appearance and tooth displacement occurs. Non infectious bone loss occurs¹³ which is in accordance with our findings. In the present case the patient presented with mobile mandibular teeth, punched out lesions of skull, multiple skin eruptions, abdominal distention as result of splenomegaly and loss of appetite leading to weight loss of 6 months duration. The underlying mandible was destroyed the skull bones involved were the calvaria where in multiple punched out lesion could be seen. When involving the mandible, severe alveolar bone resorption producing the appearance of teeth 'floating in space' can be seen as in our case. These clinical and radiographic features led to the diagnosis of Langerhans Cell Histiocytosis. Histological features of LCH include proliferation of large cells with indistinct cell borders. These cells have oval nuclei and abundant cytoplasm. The cells are oftenly arranged in sheets and are admixed with eosinophils, inflammatory cells and multinucleated giant cells. Lesions may affect a variety of other systems, including liver (20%), spleen (30%), and lymph nodes (50%). Pulmonary involvement may occur. One third of patients have mucocutaneous lesions, most frequently infiltrated nodules and ulcerated plaques, especially in the mouth, axillae, and anogenital region. Other cutaneous manifestations include extensive coalescing, scaling, or crusted papules.

The etiology of Langerhans cell histiocytosis (LCH) remains unknown. Langerhans cell proliferation may be induced by a viral infection, Specifically, human herpesvirus 6 (HHV-6) has been proposed to contribute to the initiation and/or modulation of persistent LCH. However, other studies have not shown a correlation between HHV-6 and LCH, and their reported associations may represent coincidental findings^{14, 15}

Complications appear in 30-50% of patients with Langerhans cell histiocytosis (LCH). The most common complications are orthopedic disabilities, hearing impairment, diabetes insipidus, skin scarring, and neuropsychologic defects (eg, anxiety, depression, decreased intellect)¹⁶.

The diagnosis is confirmed by histopathological examination supported by clinical and radiographic examination¹⁷. Histopathological characteristic of the lesion consists of a proliferation of Langerhans cells, which is immunohistochemically identified by the presence of the antigens S100 and CD1a¹⁸. Langerhans cells are round or oval in shape, with a vesicular nucleus, a moderate quantity of eosinophilic cytoplasm and laminated or dispersed distribution. Abundant eosinophils and other inflammatory cells such as lymphocytes and mononuclear phagocytes may be found accompanying these cells^{19, 20}.

III. Conclusion

The present case is unique where in the child was diagnosed to have a systemic problem- LCH by a pediatric dentist. Careful examination of the oral lesions is important to diagnose or to aid in the diagnosis of various systemic conditions. Pediatric dentists 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.

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Figure 1 Extra oral facial swelling Left side



Figure 2 OPG showing extensive lytic lesion of Mandible and Floating Teeth appearance

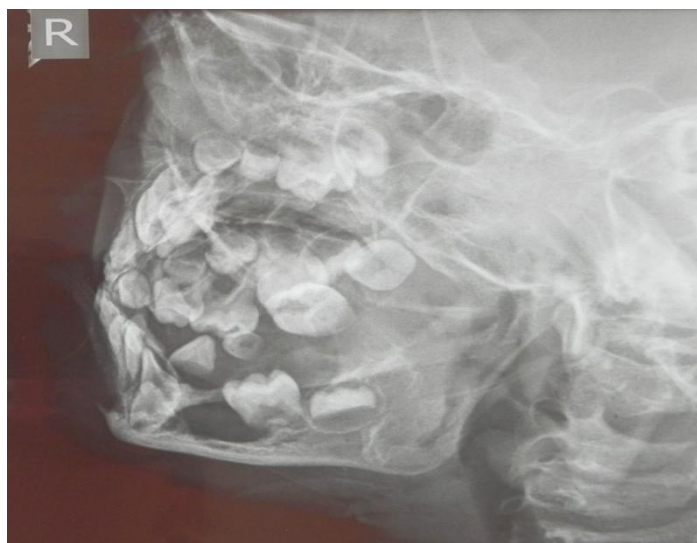


Figure 3 Mandible Right lateral view showing multiple punched out lesions

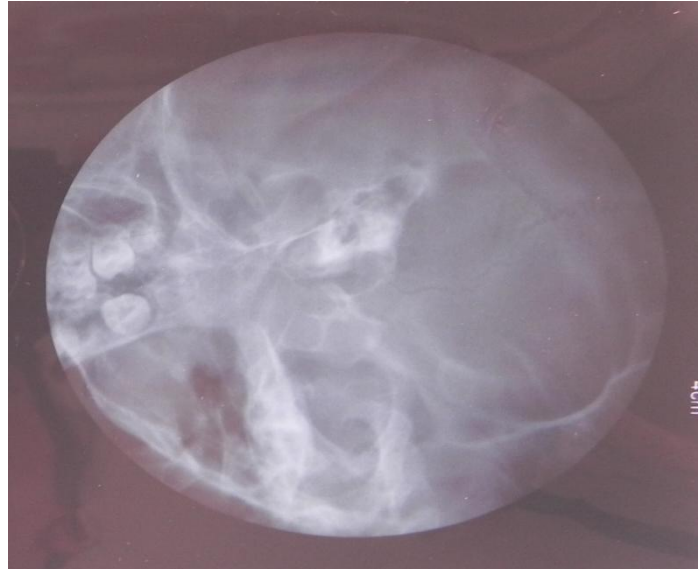


Figure 4 Lateral Cephalogram of Skull showing multiple lytic punched out lesions of skull (right side)



Figure 5 Mandible Left lateral view showing multiple punched out lesions

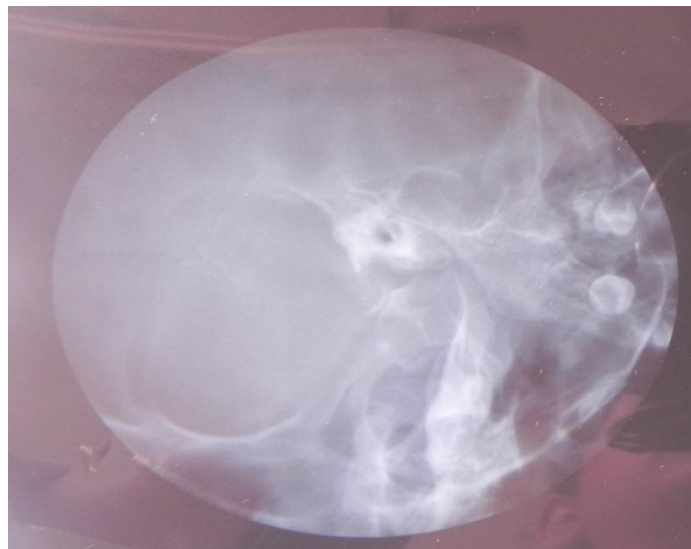


Figure 6 Lateral Cephalogram of Skull showing multiple lytic punched out lesions of skull (right side)

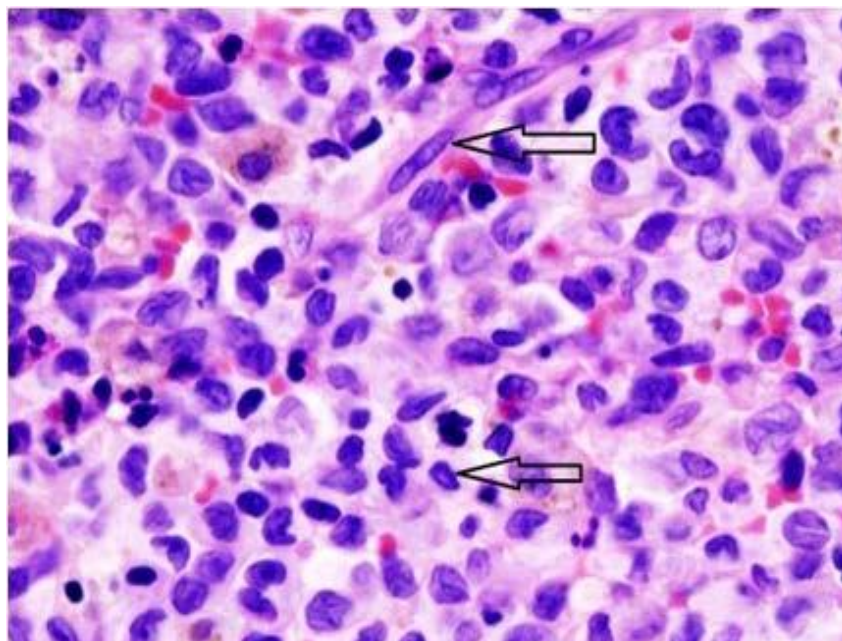


Figure 7 The Histopathological examination showing large number of Histiocytes

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