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Case Report

Clinical insights into multifocal langerhans cell histiocytosis: A detailed case report

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Abstract

Langerhans cell histiocytosis (LCH), formerly referred to as histiocytosis X, is a rare hematological disorder primarily affecting infants and young children. This condition is marked by the uncontrolled activation and proliferation of Langerhans cells, which are a type of antigen-presenting cell. Due to its low incidence, the epidemiology of LCH remains inadequately studied, with estimates suggesting 2–5 cases per million people annually. This report presents the case of a 4-year-old male diagnosed with LCH, exhibiting multiple focal lesions involving both bones and other organs. The discussion will highlight the clinical, radiological, and histopathological features of LCH, as well as the crucial role of dental surgeons in diagnosing and managing these lesions.

Keywords: Langerhans cell, Multifocal, Floating teeth apperance, Coffee bean appearance.

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1. Introduction

Langerhans cell histiocytosis (LCH) is the most prevalent histiocytic disorder, characterized by the aggregation of langerin-positive cells forming granulomatous lesions that accumulate as inflammatory infiltrates in various tissues throughout the body.[1] Previously referred to as histiocytosis X, this condition primarily affects infants and young children.[2] The exact cause of LCH remains unknown, and it has been categorized as either a neoplasm, a reactive disorder, or a result of an aberrant immune response.[3]

LCH shows a male predominance in children, with an incidence rate of approximately 8.9 cases per million children and 1-2 cases per million adults based on English literature. Although it most commonly involves the bones, LCH can affect nearly all organs in the body. In the oral cavity, LCH typically presents as an ulcerative, proliferative lesion accompanied by bleeding gums, loose teeth, and localized pain.[4] Histologically, LCH is characterized by inflammatory infiltrates containing lymphocytes, eosinophils, plasma cells, giant cells, and Langerhans cells. The definitive diagnosis of LCH is made through histopathological examination, followed by immunohistochemical analysis for confirmation.[5]

Due to its complex and variable clinical features, LCH is often misdiagnosed as an inflammatory lesion or a malignant tumour, which can lead to different treatment approaches and prognosis. Therefore, early detection and diagnosis by dental professionals are critical to managing the condition effectively and preventing disease progression.

2. Case Report

A 4-year-old male patient presented to the Department of Oral and Maxillofacial Pathology with complaints of gingival swelling and generalized tooth mobility over the past year. Notably, there were no signs of spontaneous bleeding or associated pain, and his medical history was unremarkable. The extraoral examination revealed diffuse swelling in the anterior region of the jaw, while the intraoral examination identified small nodular and pebbled swellings surrounding the lower anterior teeth. (**Figure 1**)

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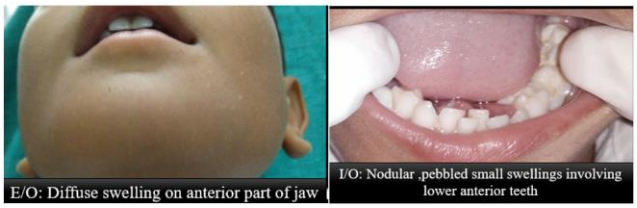

Figure 1: Extraoral and intraoral examination

Radiographic evaluation via orthopantomogram revealed extensive alveolar bone loss and diffuse lytic lesions, contributing to a "floating teeth" appearance **(Figure 2**). Further assessment with a lateral skull radiograph showed multiple lytic lesions with poorly defined margins. Complete blood tests indicated microcytic hypochromic anemia and an elevated erythrocyte sedimentation rate, while a urine analysis returned normal results.

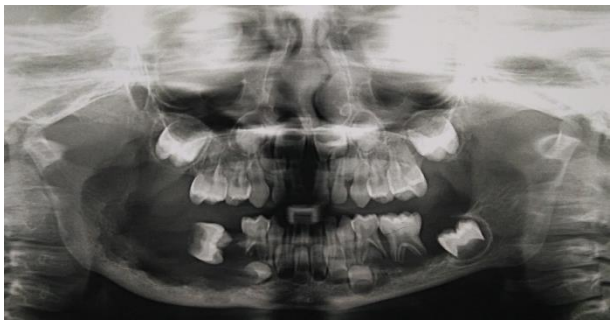

Figure 2: Diffuse lytic lesions giving "Floating teeth appearance"

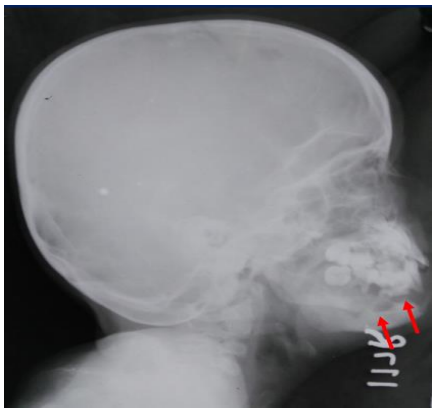

Figure 3: Lateral skull radiograph showed multiple lytic lesions

Based on the clinical and radiological findings, the case was provisionally diagnosed as either juvenile aggressive periodontitis or massive osteolysis.

Following the acquisition of informed consent, an incisional biopsy was carried out from a representative area of the lesion under local anesthesia. Histological analysis of hematoxylin and eosin-stained sections revealed a fibrovascular connective tissue extensively infiltrated by chronic inflammatory cells, mainly eosinophils and plasma cells. A notable feature was the dense proliferation of large mononuclear cells with pale, faintly staining cytoplasm, poorly defined cell boundaries, and nuclei displaying deep indentations, giving them a "coffee-bean" appearance. These cells were identified as characteristic of Langerhans cells.(**Figure 4**)

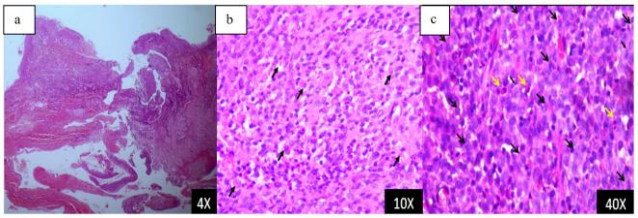

Figure 4: a): Fibrovascular connective tissue intensely infiltrated with chronic inflammatory cells; **b)**: Abundant eosinophilic infiltration; **c):** Langerhans cells with nuclear grooving

Upon reviewing the microscopic features, a diagnosis of LCH was established. Immunohistochemical analysis confirmed this diagnosis, demonstrating positivity for CD1a and Langerin (**Figure 5**).

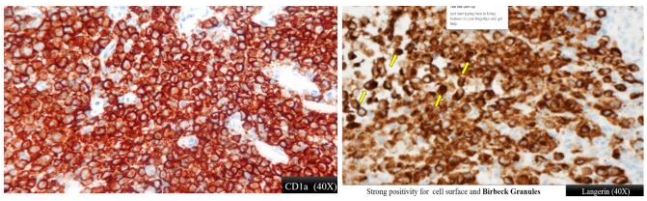

Figure 5: Immunohistochemical expression of CD1a and langerin

Consequently, the final diagnosis was confirmed as LCH. The treatment regimen included curettage, intralesional corticosteroid therapy, and radiation therapy.

One year later, the patient returned with a swelling in the left anterior neck. Following the discovery of this lesion, a full-body PET scan was recommended. The PET scan revealed soft tissue masses on the left side of the neck and involvement of the retropharyngeal node. Additionally, lytic lesions were identified in the right frontal and left parietal bones, along with multiple sub-centimetric cystic lesions in both lungs. (**Figure 6**)

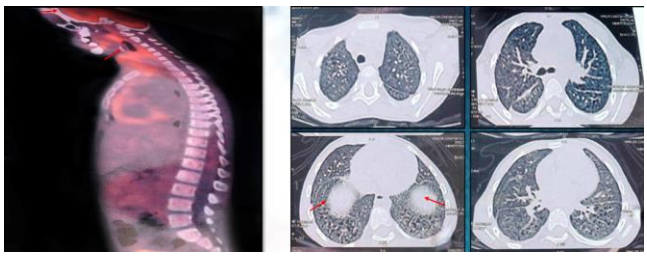

Figure 6: Full body PET scan showing lesions in retropharyngeal node, parietal bones and lungs

Integrating clinical, radiological, histopathological, and immunohistochemical findings, along with the evidence of multiorgan involvement, we arrived at a final diagnosis of multifocal LCH.

3. Discussion

Histiocytoses represent a rare and diverse group of hematological disorders, distinguished by the accumulation of histiocytes in various tissues and organs. Based on their genetic profiles and clonal characteristics, many forms of histiocytosis are now classified as myeloid neoplasms.[6] The term "histiocyte" originates from the Greek words "histos," meaning "tissue," and "-cyte," meaning "cell." Histiocytes refer to mononuclear phagocytic cells, including monocytes, macrophages, and dendritic cells, that infiltrate tissues. Previously, histiocytoses were classified primarily based on their phenotypic features, typically divided into three major categories: 1) Langerhans cell histiocytosis (LCH), 2) non-langerhans cell histiocytosis, and 3) malignant histiocytosis.[7] The Langerhans cell was first described by Paul Langerhans in 1868.[8]

Langerhans cells are dendritic mononuclear cells typically located in the epidermis, mucosal surfaces, lymph nodes, and bone marrow. Their primary role is to capture and present antigens to T-lymphocytes.[2] LCH represents a collective term for a spectrum of rare clinicopathologic disorders, characterized by monoclonal proliferation and infiltration of Langerhans type of histiocytic cells, leading to hard and soft tissue destruction.[9]

The pathological features of LCH can be divided into two primary processes. The first is an abnormal reactive process, evidenced by spontaneous remissions, favorable survival in cases with single lesions, and the involvement of multiple cytokines. The second is a neoplastic process, which is marked by multisystem involvement, higher mortality, and a positive response to chemotherapy.[11] Additionally, the recent discovery of the BRAF gene mutation (V600E) in 57% of LCH lesions further reinforces the neoplastic nature of the disease.[12]

The reported incidence of LCH ranges from 2.6 to 8.9 cases per million children younger than 15 per year, with a median age at diagnosis of 3 years,[13] which was in accordance with our case of a 4 year old child.

Historically, LCH was categorized into three distinct diseases: eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease, which represented different clinical manifestations of the same progressive systemic involvement. More recently, LCH has been reclassified based on the number and type of affected organs and the number of lesions within each organ. This classification includes various subtypes such as single-system (unifocal, multifocal, pulmonary, and central nervous system [CNS]) and multi-system forms (with or without involvement of risk organs).[1]

Oral cavity involvement in LCH often occurs at an early stage, but the initial symptoms are typically nonspecific, leading to potential misdiagnosis. Both the maxilla and mandible can be affected in LCH, with a ratio of mandible to maxilla involvement of approximately 2:1, and this may occur with or without systemic involvement. Jaw lesions can present with dull pain, regional tooth mobility, and jaw expansion.[2] Oral mucosal involvement may arise if the disease extends beyond the bone, presenting with gingival inflammation, round or ovoid ulcerated lesions, destruction of the keratinized gingiva, gingival hypertrophy, periodontal pocket formation, tooth mobility, alveolar bone expansion, and ulcers affecting the buccal mucosa, palate, and tongue.[15] In this case, the patient presented with gingival swelling in mandibular anterior region and generalised mobility since one year.

Radiographically, the lesions appear as sharply defined radiolucencies without well-corticated borders or as ill-defined radiolucent areas. Extensive alveolar bone loss around the teeth results in a "tooth floating in air" appearance.[16] Well-circumscribed, punched-out lesions may also be observed in the skull or other skeletal regions.[17,18]

Our initial diagnosis suggested chronic generalized aggressive periodontitis. However, due to the absence of pathognomonic clinical and radiographic features for LCH, the diagnosis was confirmed based on histopathological and immunohistochemical analysis.

Histopathology reveals a sheet-like proliferation of pale-staining Langerhans cells with abundant cytoplasm, indistinct cell borders, and rounded or indented "coffee-bean" shaped vesicular nuclei, without mitotic activity.[17] Eosinophils are predominant in the inflammatory infiltrate, which helps distinguish LCH from common periapical and periodontal lesions of the jaw. All three forms of LCH exhibit similar histopathological characteristics. Immunohistochemical staining for CD1a, Langerin/CD207, CD68, and S100 antibodies is diagnostic for LCH, as seen in our case.

When diagnosing Langerhans cell histiocytosis (LCH) histopathologically, several differential diagnoses should be considered due to overlapping features. Key differentials include:

1. Granulomatosis with Polyangiitis (Wegener's Granulomatosis): Characterized by necrotizing granulomas, it may show eosinophils and giant cells but lacks the distinctive Langerhans cells
2. Sarcoidosis: Presents with non-caseating granulomas and may mimic LCH histologically; however, LCH features Langerhans cells with characteristic nuclear grooves.
3. Tuberculosis: Can present granulomatous inflammation but typically shows caseating necrosis and a different immune cell composition (more macrophages and lymphocytes).
4. Fungal Infections: Such as histoplasmosis or blastomycosis can cause granulomatous lesions, often

with eosinophilic infiltrates, but lack the unique cell morphology of LCH.

5. Non-Hodgkin Lymphoma: Particularly lymphoblastic lymphoma, may show similar infiltrative patterns but lacks the distinctive Langerhans cells and typically has a more uniform appearance.
6. Leukemia: May present with skin lesions resembling LCH, but the cellular composition will differ significantly, primarily involving neoplastic lymphoid cells.
7. Other Histiocytic Disorders: Rosai-Dorfman Disease (Sinus Histiocytosis): Characterized by a large number of histiocytes, often with a "dancing" histiocytic pattern but lacks Langerhans cells and the characteristic nuclear features.

To distinguish LCH from these conditions, immunohistochemistry plays a crucial role. Key markers for LCH include CD1a, Langerin (CD207), and S100 protein, which are typically positive in LCH but negative in the other conditions mentioned. A comprehensive clinical correlation and careful evaluation of histopathological features are essential for accurate diagnosis.

Though the incidence of remission has not been formally quantified in the literature, the highest rates are generally seen in unifocal disease, with documented remissions of bone lesions occurring in sites such as the femur, orbit, intracranial bones, maxilla and mandible.[18] Recurrences have also been observed, but rarely in a different site and usually within 12–18 months after initial diagnosis.[19] Similar to literature, our case had also shown recurrence within one year of diagnosis, with presentations of neck swelling.

Hence, complete physical and hematological examinations along with, urine tests, and, complete skeletal radiographic survey, PET scan were advised to check for multiorgan involvement. Our case showed involvement of multiple organs namely, retropharyngeal nodes, frontal bone, parietal bone, skull and lungs. Hence based on all the finding we arrived at a diagnosis of LCH, multifocal variant.

Treatment of Langerhans cell histiocytosis (LCH) varies based on the severity and extent of the disease. For localized forms, such as solitary bone lesions, observation or surgical intervention may be sufficient. More extensive or symptomatic cases often require systemic therapy, including corticosteroids, chemotherapy, or targeted therapies like BRAF inhibitors, particularly in cases with BRAF mutations. Supportive care and management of complications are also essential. Multidisciplinary approaches involving pediatricians, oncologists, and specialists in hematology are crucial for optimizing outcomes, especially in high-risk or multi-system disease.

4. Conclusion

This case report illustrates the complexities of diagnosing and managing oral Langerhans cell histiocytosis (LCH) in a pediatric patient. The initial presentation of gingival swelling and dental mobility, alongside characteristic radiological and histopathological findings, underscored the need for a thorough evaluation to differentiate LCH from other conditions like juvenile aggressive periodontitis. Despite initial treatment with curettage and corticosteroid therapy, the subsequent identification of multifocal involvement emphasizes the unpredictable nature of LCH. This case highlights the importance of early diagnosis and continuous monitoring, advocating for heightened awareness among dental professionals to ensure timely intervention and better outcomes for affected patients.

5. Source of Funding

None.

6. Conflict of Interest

None.

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