Case Report

Atypical jaw swelling in children: An unusual clinical spectrum of Langerhans cell histiocytosis

Sithara K, Usha Balan, Rajeesh Mohammed PK, Akhila S. Stanly

Department of Oral Pathology and Microbiology, KMCT Dental College, Mukkam, Calicut, Kerala, India

Abstract

Langerhans cell histiocytosis (LCH), also called histiocytosis X or eosinophilic granuloma, is a local or systemic unusual clonal proliferative disorder of Langerhans cells. It has a wide spectrum of clinical presentations and can occur in any age group with predominance in children and young adults. This article presents a rare case of LCH in a 2-year-old girl child which was provisionally diagnosed as an infection of the jaw bone of unknown etiology. Correlating the clinical, radiologic, and histologic features with immunohistochemical analysis aided in arriving at a definitive diagnosis of LCH. Oral manifestations being the earliest presentation seen in around 5%–75% of LCH cases emphasize the role of a dentist in the early detection of this lesion. A myriad of clinical spectra due to pathologic infiltration of Langerhans cells into various systems necessitates oral diagnosis to be followed by a full body scan to detect any systemic involvement. Advanced targeted therapies can improve the survival rate and quality of life in patients with LCH.

Keywords: Atypical jaw swelling, CD1 antigens, histiocytosis X, Langerhans cell histiocytosis

Address for correspondence: Dr. Sithara K, Department of Oral Pathology and Microbiology, KMCT Dental College, Mukkam, Calicut, Kerala, India.
E-mail: sitharakoraprath@gmail.com

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INTRODUCTION

Histiocytosis refers to a group of rare proliferative diseases of the reticuloendothelial system. Langerhans cell histiocytosis (LCH), also called as histiocytosis X or eosinophilic granuloma, is characterised by aberrant growth of both mature eosinophils and specialised bone marrow-derived antigen-presenting dendritic cells. The term "Histiocytosis X" was introduced by Lichtenstein, and the "X" indicated an uncertain cell of origin.[1]

LCH can occur at any age with the greatest incidence in children younger than 15 years of age[2] with approximately 5–10 cases per million per year and in adults with an incidence of 1–2 cases per million per year with a male-to-female ratio of 1.2:1. LCH can involve a single organ or multiple organs[3] and has three main components: Letterer–Siwe disease, Hand– Schuller–Christian disease, and eosinophilic granuloma.[2]

It can involve sites like the skin (50% cases), bone, mucus membrane, and various internal organs, mainly the liver, spleen, lung, and brain.[4] Lytic bone lesions (80% of cases), rash (20–40% of cases), soft tissue swelling (frequently near bony lesions), external ear discharge, lymph node or thymic enlargement, and gingival hypertrophy with early tooth eruption are some of the characteristic clinical presentations seen in LCH. Severe systemic involvement forecasts a higher risk of morbidity and mortality in LCH.

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Early diagnosis and improved treatment strategies such as MAPK inhibitors with chemotherapy or epigenetic modifiers or anti-apoptotic agents are essential to safely cure patients with LCH and associated disorders.[3]

This report describes a case of Langerhans histiocytosis in a female child with unusual involvement of the ramus and condylar region.

CASE HISTORY

A 2-year-old girl child was referred to our institution by a general dentist with a complaint of painful swelling on the left side of the face since 4 months. It was provisionally diagnosed as osteomyelitis of the jaw bone and was treated with antibiotics and analgesics. Swelling slightly subsided with medication but relapsed following discontinuation. There was no relevant medical history, and the patient was moderately built and nourished.

Clinical examination revealed a diffuse swelling on the left side of the face extending 3 cm antero-posteriorly from the midline to the angle of mouth and superio-inferiorly from the infra-orbital region to the inferior border of the mandible. The skin over the swelling was normal with no evidence of pus discharge and bleeding [Figure 1]. Intra-orally, there was no vestibular obliteration and the swelling was tender on palpation. Level 2 lymph nodes were palpable clinically.

Orthopantomogram (OPG) revealed osteolytic areas in the left mandibular ramus and condyle [Figure 2].

Magnetic resonance imaging (MRI) scan of the neck revealed a well-defined, expansile heterogeneously T2 hyperintense lesion with heterogeneous post-contrast enhancement involving the left mandibular ramus and condyle. There was cortical erosion in the inferolateral aspect of the lesion, and it was projecting into the left parotid gland. There were multiple enlarged level 2 lymph nodes, and the report was suggestive of an aggressive lesion [Figure 3]. Based on the clinical and radiological findings, differentials considered were "osteomyelitis of jaw bone", "intraosseous squamous cell carcinoma", and other malignancies such as "Ewings sarcoma", "leukemia", and "myeloma".

An incisional biopsy was performed and sent for histopathological examination. Tissue bits were processed for microscopic evaluation [Figure 4].

Haematoxylin and eosin-stained sections revealed mild to moderately cellular stroma with areas of necrosis. Stroma showed numerous plasma cells, lymphocytes, histiocytes, bi-lobed eosinophils, and sheets of extravasated RBCs. A few cells with a pale eosinophilic cytoplasm containing oval nuclei with grooves or indentations were scattered within the stroma which were resembling Langerhans cells [Figure 5]. These findings were suggestive of LCH, and the differentials considered were other histiocytic/round cell tumours.

Immunohistochemical analysis for S100 and CD1a markers was performed to confirm the diagnosis of LCH. Diffuse positivity was observed for S100 marker, indicating the possibility of LCH and mononuclear cells revealed strong expression for CD1a, hence confirming the diagnosis [Figure 6]. The patient was referred to the regional cancer centre to rule out any systemic involvement and for advanced treatment.

DISCUSSION

Histiocytoses are disorders depicted by the accumulation of cells that are believed to be derived from dendritic cells or macrophages. Jean-Francois Emile *et al.*[5] have

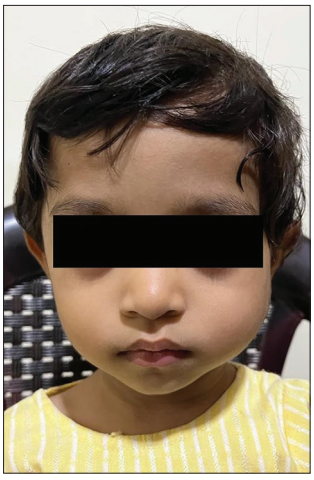

Figure 1: Clinical image shows diffuse swelling on the left side of the face

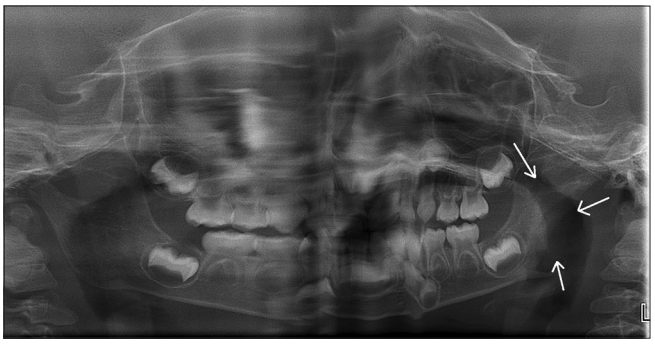

Figure 2: OPG image shows an osteolytic area in the left mandibular ramus and condylar area

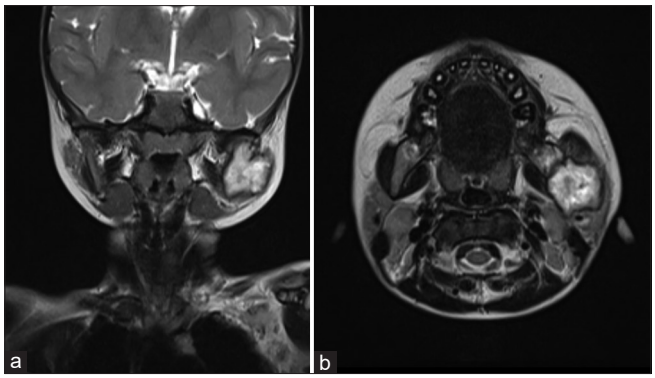

Figure 3: MRI images show well-defined, expansile heterogeneously T2 hyperintense lesion with heterogeneous post-contrast enhancement involving the left mandibular ramus and condyle: (a) Coronal view and (b) Axial view

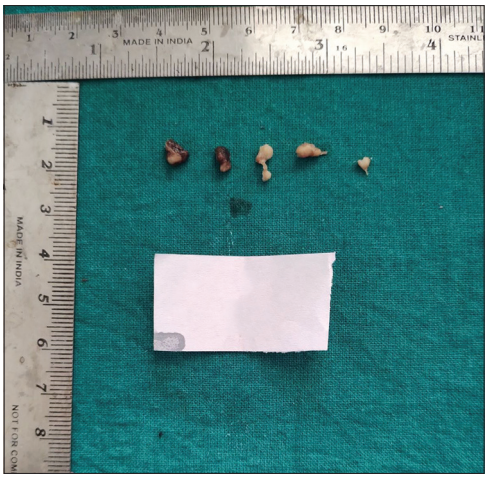

Figure 4: Gross image shows multiple bits of soft tissue specimens which are creamy and dirty brown in colour

described five groups of histiocytoses based on clinical, radiographic, pathological, phenotypic, genetic, and/or molecular features as L (Langerhans), C (cutaneous and mucocutaneous histiocytosis), R (Rosai-Dorfman disease and miscellaneous non-cutaneous, non-Langerhans cell histiocytoses), M (malignant histiocytosis), and H (haemophagocytic lymphohistiocytosis and macrophage activation syndrome) groups; in this, LCH pertains to L group.

As per the guidelines of the Histiocyte Society, depending on the organs involved, LCH has been classified into a localised and disseminated form. The exact aetiology and pathogenesis of LCH still remain unclear.[6] A few cases of familial LCH have been reported in the literature, but there is no evidence of genetic susceptibility identified to date.[5]

Earlier, it was considered as a reactive lesion, but recent literature describes it as an inflammatory myeloid neoplasia. There is clonal expansion of myeloid precursors that differentiate into $CD1a^{+}$/CD207 + in LCH lesions.[7] Nearly 60% cases of LCH exhibited BRAF V600E mutation repeatedly, which regulates cell survival, motility, proliferation, and cell differentiation in cell signals.[8,9] A few studies have found a correlation between the presence of *BRAF* V600E in blood and a higher rate of recurrence.[10]

The degree and severity of LCH are determined by the level of differentiation of the myeloid precursor in which the activating MAPK mutation originates. This was supported by a model of "Misguided Myeloid Differentiation" which is supported by observations in LCH patients and mice research.[3]

The common locations for LCH are the head and neck, especially skull bones and jaws. Gingiva and hard palate are the most common intra-oral sites. The clinical spectrum varies from a simple solitary lytic lesion of the bone, having a better prognosis to a highly fatal form that is disseminated and leukemia-like. The usual clinical symptoms seen are skin rash, gingival hypertrophy, lymphadenopathy, disturbed balance, and memory problems. Oral symptoms usually turn up prior to any other symptoms and manifest as a painful, ulcero-proliferative lesion with gingival bleeding and mobile teeth. But the present case appeared as a diffuse swelling on the left side of the face without any evidence of vestibular obliteration, gingival ulceration, pus discharge, and bleeding, which are uncommon findings in the case of LCH. Hence, oral lesions have to be investigated meticulously by considering all possible differential diagnoses for early diagnosis of LCH.

The wide range of clinical presentation of LCH makes diagnosis of this lesion challenging. LCH does not show specific radiographic characteristics and mimics periodontal disease, osteomyelitic lesions, and malignancies such as intra-osseous squamous cell carcinoma, Ewings sarcoma, leukemia, and myeloma. Such malignancies are very rare in young children, and histopathological diagnosis is essential in excluding the above differentials. "Intra-osseous squamous cell carcinoma" commonly shows a solitary ill-defined radiolucency, and it may be associated with a soft tissue mass. Sequestrum is a "hallmark" manifestation of "osteomyelitis",[9] and these features are not observed in the present case.

Radiographically, LCH usually shows sharp and punched-out radiolucencies; associated teeth may appear as "floating in air"; when alveolar involvement is substantial.[6] The present case appeared as a radiolucency which was involving only the ramus and condyle and developing 36

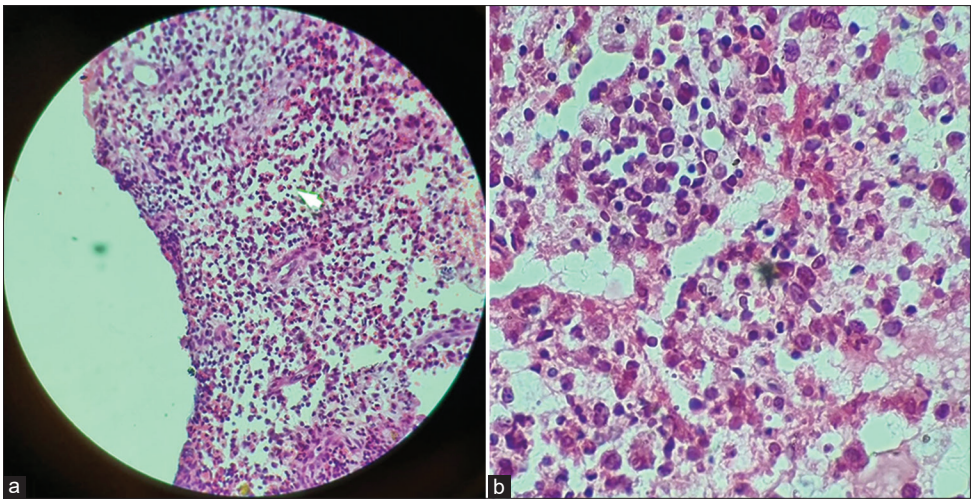

Figure 5: (a) Histopathological image shows numerous plasma cells, lymphocytes, histiocytes, eosinophils, and sheets of extravasated RBCs (H and E stain, x100). (b) A few cells with oval nuclei and an abundant pale eosinophilic cytoplasm and cells with grooves are seen scattered within the stroma (H and E stain, ×400)

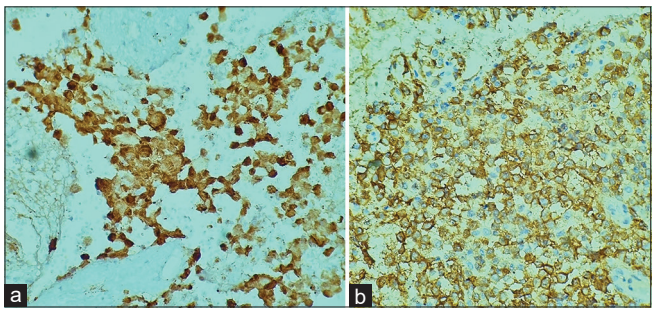

Figure 6: (a) IHC image shows S100 protein positivity (×400). (b) IHC showing CD1a antigen positivity (×400)

was seen intact in the OPG and in close proximity to the radiolucent area.

Microscopically, Langerhans cells in LCH are described as generally large, 15 to 25 μm in size, and round to oval in shape and lack the branching that characterises classic inflammatory $CD1a^+$ dendritic cells. The nucleus appears with a "coffee-bean" nuclear groove. Other salient features are an inflammatory milieu of macrophages, eosinophils, and small lymphocytes, rarely plasma cells admixed with the Langerhans cells.[8] The present case showed a few cells with pale eosinophilic cytoplasm containing oval nuclei with grooves or indentations scattered within the stroma resembling Langerhans cells and hence suggestive of LCH.

Immunohistochemistry (IHC) is considered to be the gold standard method for the definitive diagnosis of LCH[6] to rule out other possible histiocytic or round cell tumors. Positive staining with both S100 and CD1a is essential for its confirmatory diagnosis. Other indicating factors which deliver specific diagnosis are Langerin (CD207), Vimentin, CD45, ecto-ATPase, and the simultaneous expression of CD68, MIB-1, peanut agglutinin, and placental-like alkaline phosphatase.

Histiocytic lesions such as juvenile xanthogranuloma family (JXG) and Rosai-Dorfman disease (RDD) also show similar clinical and histological features as LCH and have to be precluded. JXG has an oval nucleus, an inconspicuous nucleolus, and a variable amount of eosinophilic cytoplasm. The cells are variably spindled with the presence of multi-nucleated Touton giant cells. Immunophenotypically, cells are consistent with negativity for CD1a and CD207, with light and variable staining for S100.

Areas of RDD-type pathology have been seen in patients with LCH. Plasma cells are usually abundant, and the present case also showed numerous plasma cells. But interestingly, even if the RDD cell selectively stains strongly for S100, other confirmatory markers such as CD1a/CD207 are absent in RDD cases;[8] hence, positive staining with S100 and CD1a is of paramount importance in the definite diagnosis of LCH, and the present case also revealed the same. Electron microscopy can be considered as an alternative for IHC to find out the presence of Birbeck granules.[6]

The association between LCH and other malignancies [acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lung carcinoma, thyroid carcinoma, Hodgkin and non-Hodgkin lymphomas] has also been described, with frequencies varying from 2.6% in children to 32% in adults. The same oncogenic mutations are reported in both LCH and ALL, or both have an identical

T-cell receptor or immunoglobulin rearrangement. This suggests the evidence of a clonal relationship between LCH and ALL, which emphasises the pertinence of targeted therapy in the case of LCH.[7]

The treatment of LCH includes anti-inflammatory agents such as steroids and cytostatic agents, such as vinblastine. Recently, newer therapeutic strategies have been developed, such as MAPK inhibitors, for severe and refractory forms of the disease.[10]

Further research is warranted to develop enhanced therapeutic approaches for the safe management of LCH and its related disorders. Since a majority of patients present with oral symptoms, it highlights the significance of dentists in the early detection of this disease and facilitating appropriate referrals for systemic evaluation and improved treatment strategies.

Research in newer improved therapeutic strategies is of paramount importance to safely cure LCH and its related disorders. Since patients present with oral symptoms initially, the role of the dentist in identifying this disease at the earliest and providing adequate referral for systemic evaluation and better treatment strategies are emphasised.

Key Messages

Absence of gingival ulceration and involvement of ramus and condyle is an atypical manifestation of LCH.

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Patient informed consent

Obtained the signed informed consent form from the patient's father since patient was a 2 year old child, in the presence of a witness.

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Conflicts of interest

There are no conflicts of interest.

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