

CASE REPORT

Langerhans cell histiocytosis in a pediatric patient: A typical presentation with oral manifestations

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Key Clinical Message

Langerhans cell histiocytosis (LCH) is a rare hematological disorder characterized by abnormal proliferation of Langerhans cells. Head and neck region is commonly involved with oral manifestations appearing first in many instances. A thorough knowledge of the disorder and an interdisciplinary approach warrant for the better outcome of the condition.

KEYWORDS

Langerhans cell, Langerhans cell histiocytosis, oral manifestations

1 | INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare hematological disorder characterized by intense and abnormal proliferation of bone marrow-derived immature myeloid dendritic cells; Langerhans cell histiocytes in the skin, bone, lymph nodes, and other organs.¹ Although, due to its low occurrence, limited information on the epidemiology of LCH is available, an estimated five to nine cases per million in children <15 years of age, and 1 case per million in patients >15 years of age have been reported.²

Langerhans cells are primary antigen-processing dendritic cells originating from bone marrow myeloid precursors and represent the most peripheral extension of the immune system. In contrast to normal Langerhans cells, Langerhans cell histiocytes are immature dendritic cells

which lack dendritic cell processes and have a round to ovoid, epithelioid morphology. Also, in spite of their activated state, their ability to present antigens is either absent or rarely observed. However, both these cells possess Birbeck granules and are positive for S100 protein, CD1a, and CD207 (langerin) markers, while being negative for macrophage markers (CD68, lysozyme, CD14, CD163).³

Depending on the different clinical manifestations, LCH had been classified conventionally by the International Histiocyte Society into three different types: type I—Eosinophilic granuloma (chronic focal LCH), type II—Hand-Schüller-Christian disease (chronic disseminated LCH), and type III—Letterer-Siwe disease (acute disseminated LCH).⁴ However, because clinical findings are widely manifested, the disease has also been classified into unifocal and multifocal forms; depending on

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the extent of its spread throughout the body. The unifocal form presents only one destructive lesion in an organ, affecting bones or skin (80% of cases), liver, spleen, brain, and lymph nodes more frequently.⁴ The disease manifests itself in a variety of ways, from isolated disease that resolves on its own to life-threatening multisystem disease, with a 20% mortality rate.⁵

The involvement of head and neck region is quite common in LCH, particularly the bones of skull and jaws. The oral soft tissue lesions are also common and are mostly seen on the hard palate and gingiva. Since the symptoms of LCH may first appear in the oral cavity before occurring elsewhere in the body, a thorough knowledge of the clinical presentation of the disease is important.¹

Treatment of LCH is carried out by surgical excision, chemotherapy, radiotherapy, or combination of these modalities. For unifocal bone disease, local excision with or without radiation therapy can be carried out with more than 95% disease-free survival rate. However, there are chances of relapse in about 10% of cases. In cases of multifocal bone disease, a combination of surgery, chemotherapy, and radiation therapy can be done with disease-free survival in about 91% of the patients. The relapse rate is higher with multifocal bone disease (76%) with a mortality rate of 3%.³

Awareness among clinicians regarding the clinical, histological, and immune-histopathological features of the disease will help in early diagnosis and treatment for better prognosis. Thus, this report aims to present a case of Langerhans cell histiocytosis with the oral and dermal manifestations seen in a pediatric patient.

2 | CASE REPORT

A 5-year-old male presented with a chief complain of loose teeth bilaterally in the lower jaw since 3 months. On evaluation of the history, the parents summarized that the child first complained of pain while eating and occasional bleeding from gingiva 6 months back. Soon the parents also noticed swelling and structural distortion in the fingernails on left hand along with pus discharge from left ear. The parents also added that they had brought the child for check-up 6 months earlier but due to COVID-19 pandemic, no active intervention was possible.

On intraoral examination, multiple ulcerations were present bilaterally on hard palate, extending posteriorly with the largest lesion measuring $1.5 \times 1 \text{ cm}^2$ in maximum dimension (Figure 1A). After 6 weeks, the ulcer showed central area of creamish white slough of variable thickness with erythematous periphery (Figure 1B). On further examination, Grade III mobility was present in relation to primary mandibular right and left first molar with gingival recession and grade II mobility were evident on primary mandibular right and left second molar. Also, the marginal and attached gingiva in relation to primary mandibular right and left second molar were inflamed (Figure 2).

On clinical examination, there was blackish discoloration and destruction of nail plate of middle and little finger of right hand and all the fingers of left hand (Figure 3). Also, watery discharge was seen from the left ear.

Panoramic radiograph was advised; however, the image was distorted as the patient was uncooperative.

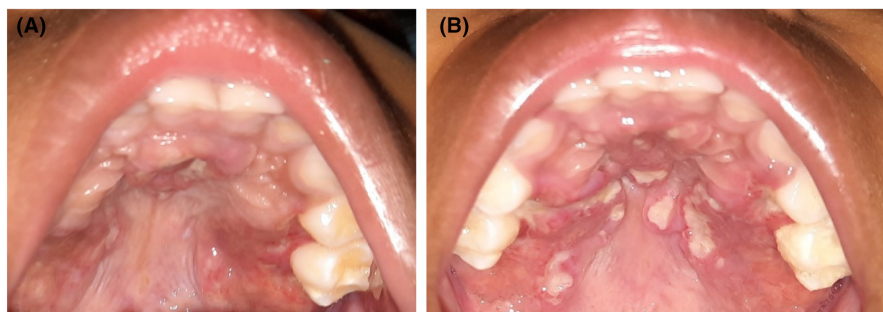


FIGURE 1 (A) Multiple ulcerated lesions present bilaterally on the hard palate; (B) Creamish white slough with erythematous periphery observed after 6 weeks.



FIGURE 2 Gingival recession in relation to 74 and 84 and gingival inflammation in relation to 75 and 85 (R: Right, L: Left).



FIGURE 3 Blackish discoloration and destruction of nail plate of middle and little finger of right hand (R) and all fingers of left hand (L).



FIGURE 4 *Site from where biopsy specimens were obtained (1-week follow-up).

Interdental bone loss in relation to primary maxillary left first and second molar and primary mandibular right and left first and second molar with distortion of follicle of permanent mandibular left first premolar was observed.

Computer tomography (CT) scan of the head and neck region was performed under midazolam sedation which showed mild soft tissue thickening in the bilateral lateral aspect of hard palate. However, no obvious growth or erosion of palate was observed.

The blood investigation showed elevated level of alkaline phosphate (387 U/L) (normal range: 35–130 U/L) and serum glutamic-oxaloacetic transaminase (SGOT: 51 U/L) (normal range: 10–35 U/L). Also, there was slight increase in serum glutamic-pyruvic transaminase (SGPT: 47 U/L) (normal range: 09–43 U/L) and platelet (475,000 cell/mm) (normal range: 150,000–400,000 cells/mm).

The clinical diagnosis of granulomatous disease was suggested, and incisional biopsy was planned under general anesthesia. Two soft tissue specimens from hard palate and junction between hard and soft palate, measuring 17×10×4 mm and 9×8×6 mm respectively, were obtained, fixed in 10% neutral buffered formalin, and sent for routine histopathological processing (Figure 4). The processed tissue was embedded and sectioned into 3 μm sections and stained with routine hematoxylin and eosin stain.

On histopathological examination, a highly cellular connective tissue stroma with numerous scattered round to polygonal-shaped cells with pale cytoplasm was evident (Figure 5A,B). On higher magnification (oil immersion), a characteristic coffee bean-shaped and oval nuclei which were folded or indented with some cells having grooved nuclei were observed (Figure 5C,D). Background stroma was abundant with eosinophils (Figure 5D). Overlying

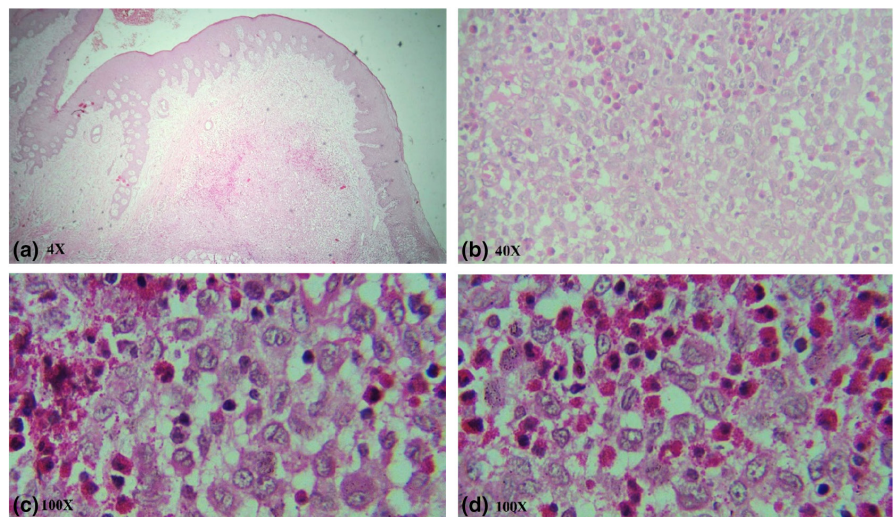


FIGURE 5 Histopathological presentation with oval to polygonal cells with pale cytoplasm and characteristic reniform and grooved nuclei (H and E Stain).

epithelium was para to non-keratinized stratified squamous type with irregular rete ridges. The histopathological features along with clinical findings and altered serum biochemical parameters were suggestive for Langerhans cell histiocytosis as a probable diagnosis.

Furthermore, on immune-histochemical analysis histiocytic cells showed positivity to CD1a, Langerin (CD-207), and S-100 markers confirming the diagnosis of LCH. 99MTC-MDP bone scan of the patient revealed normal bone with no evidence of skeletal metastasis (Figure 6). Ultrasonography of the upper abdomen and pelvic region showed normal scan with no spleen and liver involvement.

A final diagnosis of Langerhans cell histiocytosis—single system multifocal disease was made, and the patient

underwent chemotherapy (Vinblastine + Prednisolone) for 43 weeks. The lesions have healed, and no new lesions have developed in 1-year follow-up visit (Figure 7).

3 | DISCUSSION

Langerhans cell histiocytosis, formerly known as histiocytosis X, is a term used to describe a group of clinicopathological conditions marked by a monoclonal proliferation of histiocyte-like cells followed by varying numbers of eosinophils, lymphocytes, plasma cells, and multinucleate giant cells on histological examination.⁶ The histiocytes present here is recognized as Langerhan

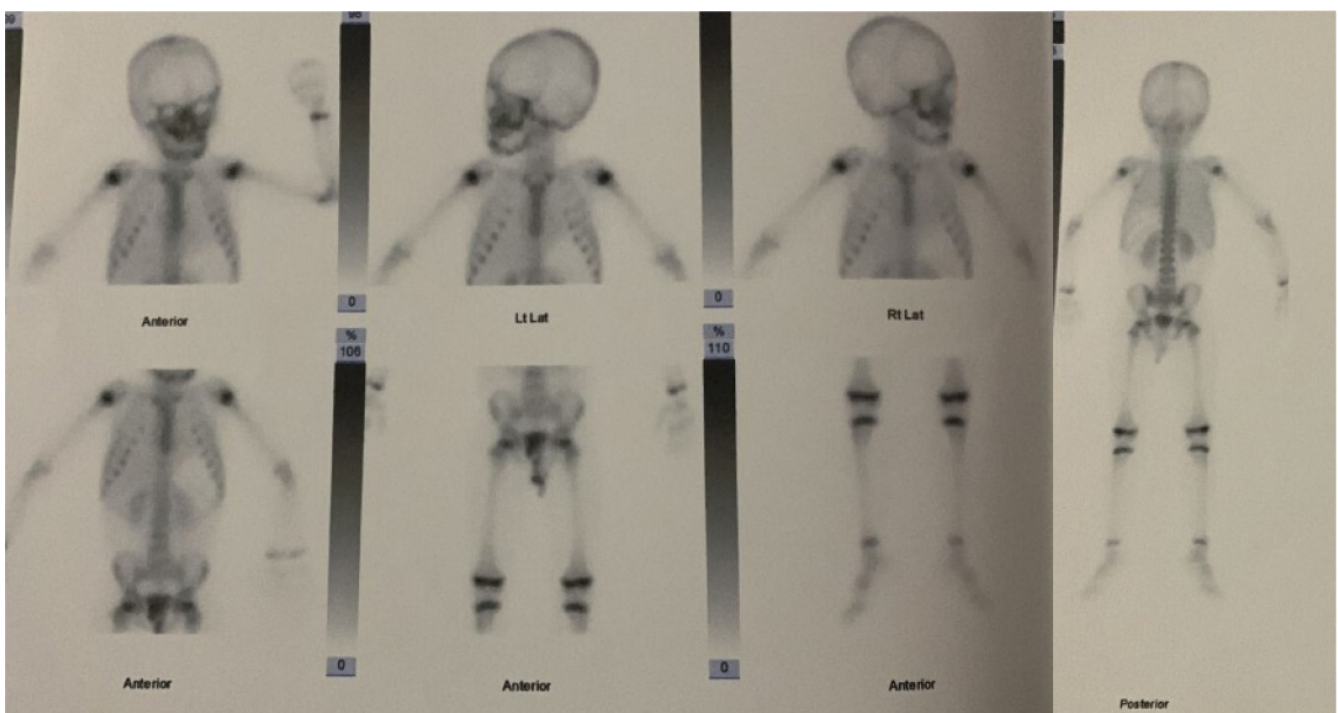


FIGURE 6 99MTC-MDP bone scan revealing normal bone with no evidence of skeletal metastasis.



FIGURE 7 Improvement in the lesions of palate and finger nails 1 year after completion of treatment (R: Right, L: Left).

cells. Langerhans cells are dendritic mononuclear cells which are generally found in the epidermis, mucosa, lymph nodes, and bone marrow. They generally present antigens to T-lymphocytes; however, literature review of LCH indicates that Langerhans cell histiocytes proliferate monoclonally, resulting in the destruction of hard and soft tissues.⁷ Despite significant progress in medical fields, the pathophysiology of LCH remains unclear; suggested mechanisms are the product of either an abnormal auto-immune response or a neoplastic process.⁵

LCH can affect people of wide age range, but it is more common in children under the age of 15 years, with a peak occurrence at 2–4 years and a male predilection that is twice as high as that of females.² The present case was reported in a 5-year-old male child. The jaws are involved twice as commonly as the oral soft tissues. The mandible is three times more frequently affected than the maxilla with a higher predisposition for the posterior regions of the jaws than the anterior regions.³ These findings are similar to the present case where mandibular posterior regions were affected more. In about 5%–75% of patients, oral manifestations are the first signs and symptoms and sometimes the only symptom of LCH, thus, prompting the patient to seek treatment from a dentist.⁸ Eden P et al., reported in a case series ($n = 13$) that seven of the cases showed intraosseous lesion in the posterior region of the jaw and oral mucosal involvement (tongue, buccal mucosa and gingiva).⁹ Sore throat, halitosis, gingivitis, gingival hypertrophy, unpleasant taste, tooth mobility with alveolar expansion, jaw pain, facial swelling, mental nerve anesthesia, and inability of extracted tooth sockets to heal are some of the oral symptoms. The loss of supporting alveolar bone may be mistaken for advanced periodontitis.⁸ In the present case, palatal ulcer, tooth mobility, pain, and bone loss were the features in consideration.

According to Krooks et al., the involvement of nails is uncommon, but can be seen as subungual pustules, hemorrhage, purpuric striae, purulent discharge, longitudinal grooving, onycholysis, paronychia, and pitting.⁵ In the present case as well, changes in the nails were evident. LCH lacks the pathognomonic clinical or radiographic features; thus, a definite diagnosis is based on a histologic and immune-histochemical examination, where CD1a, Langerin (CD207), and S-100 protein positivity is common.¹⁰ S-100 is a calcium-binding protein present in the nucleus and cytoplasm of glial and Schwann cells, melanocytes, chondrocytes, adipocytes, and myoepithelial cells and is positive for all tumors derived from these cells. CD1a is expressed on Langerhans precursors, Langerhans cells and thymic cortical T cells, whereas Langerin is a type II transmembrane cell surface receptor produced by Langerhans cells which helps

in differentiating Langerhans cell histiocytosis from other non-Langerhans cell histiocytic proliferations. As in our case immunostaining was positive for CD1a, Langerin, and S-100, it helped in confirming the diagnosis of LCH.

The treatment of this multifocal disease includes a combination of surgical excision, chemotherapy and/or radiation therapy. In the present case, only chemotherapy was attempted. In the recent follow-up, no new lesion or recurrence has been observed. However, a long-term follow-up is warranted to elicit the nature of this multifocal disease.

The dentists are usually the first clinicians to examine the child's oral cavity, hence, awareness regarding the varied manifestations of this rare condition is important for early diagnosis and appropriate referral of the patient. Also, multidisciplinary approach is necessary for the overall management and well-being of the child. Since, the lesions present in LCH may be confounded with a malignant process, histological, and immune-histochemical tests play a vital role in confirming the diagnosis.⁴

4 | CONCLUSION

Langerhans cell histiocytosis is a disease with a wide range of clinical symptoms. LCH, being a rare condition, is at a high risk of being misdiagnosed or underdiagnosed. A thorough history, clinical examination, appropriate investigations, and a sound knowledge of the condition helps to make a correct diagnosis at an early stage, thus reducing the morbidity and mortality associated with this pathology. An interdisciplinary approach is also imperative for the success of the management of the condition.

AUTHOR CONTRIBUTIONS

Royasa Shakya: Writing – original draft. **Bandana Koirala:** Writing – review and editing. **Ashok Dongol:** Writing – review and editing. **iccha Kumar Maharjan:** Writing – review and editing. **Shashi Keshwar:** Writing – review and editing. **Neetu Jain:** Writing – review and editing. **Ashish Shrestha:** Writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

CONSENT

Written informed consent was obtained from the patient's parents to publish this report in accordance with the journal's patient consent policy.

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