**Oral and Cutaneous Involvement in Langerhans Cell Histiocytosis: A Systematic Review**

### ****Abstract****

**Background:**
Langerhans Cell Histiocytosis (LCH) is a rare disorder characterised by clonal proliferation of Langerhans cells, with potential involvement of multiple organ systems, including the skin and oral cavity. Oral and cutaneous lesions may represent early signs of systemic disease, emphasising the importance of their recognition.

**Aim:**
To systematically review and evaluate demographic data, clinical features, prognostic indicators, and treatment outcomes of oral and cutaneous involvement in LCH.

**Materials and Methods:**
A comprehensive literature search was performed using PubMed Central, Google Scholar, and the Cochrane Central Library, adhering to PRISMA-P (2015) guidelines. Keywords included “cutaneous involvement”, “oral involvement”, and “Langerhans cell histiocytosis”. Articles were limited to case reports and case series published in English from 2005 to December 2024. Studies with isolated oral or cutaneous involvement, abstracts, and incomplete data were excluded. A total of 68 relevant studies were identified and analysed.

**Results:**
Cases demonstrating both oral and cutaneous LCH involvement were extracted and categorized based on demographic parameters, clinical presentation, histopathological features, therapeutic interventions, and outcomes. From the refined search, 11 studies reported dual involvement (oral and cutaneous) between 2005 to December 2024. Prognosis varied based on systemic spread, early diagnosis, and intervention strategies.

**Conclusion:**
Oral and cutaneous manifestations can serve as early diagnostic indicators of LCH. Comprehensive documentation and awareness of such presentations are crucial for prompt diagnosis and treatment. Systematic evaluation of case reports reveals the significance of multidisciplinary management in improving outcomes.

**Keywords**

Langerhans cell histiocytosis, oral involvement, cutaneous involvement, oral cavity

**Introduction**

Histiocytic disorders arise from mononuclear histiocytes, which are components of the macrophage system [1]. These cells normally function within the reticuloendothelial system. When their precursors proliferate in the bone marrow, conditions such as monocytic leukaemia may develop. Excessive proliferation of immature histiocytes in tissues is characteristic of histiocytic medullary reticulosis. Historically, the abnormal proliferation of mature histiocytes was known as histiocytosis X [2].

The term "histiocytosis X" was first introduced by Lichtenstein in 1953 to describe an enigmatic histiocytic disorder of uncertain origin. He observed that the condition could not be definitively classified as neoplastic, inflammatory, or a lipid storage disorder. Over time, researchers identified three distinct clinical manifestations that shared the same histological features. This disorder has been known by various names, including eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian syndrome, Hashimoto-Pritzker disease, self-healing histiocytosis, cutaneous histiocytosis, Langerhans cell granulomatosis, and non-lipid reticuloendotheliosis [3].

Presently, the condition is referred to as Langerhans cell histiocytosis (LCH), as it arises from the abnormal proliferation and migration of specialised dendritic skin cells first identified by Paul Langerhans in 1868. Recent research suggests that LCH may be linked with immune system dysfunction [5]. These Langerhans cells, originating from CD34+ stem cells in the bone marrow, travel through the bloodstream to various tissues, including the skin, lungs, thymus, lymph nodes, and gastrointestinal tract. A distinctive histopathological characteristic of Langerhans cells is the presence of Birbeck granules in their cytoplasm, which were identified nearly a century after the cells themselves. [7]

According to the World Health Organization (WHO) classification, LCH is categorised among malignant histiocytic diseases. Although it predominantly affects bones, it can also involve multiple organ systems and often presents as a multisystem disorder. LCH may manifest as a single bone or lung lesion, be restricted to the skin (Lau et al., 2006), or evolve into a severe, life-threatening disease that affects multiple organs, including the skin, bones, lymph nodes, lungs, liver, spleen, endocrine glands, oral cavity and central nervous system [3]. The exact cause of LCH remains unclear, although potential contributing factors include neonatal infections, inadequate childhood immunisation, exposure to solvents, and thyroid dysfunction. The disseminated form of LCH has been associated with acute lymphoblastic leukemia and malignant lymphomas, while the pulmonary variant in adults is strongly correlated with smoking. The congenital form of the disease is rare, and genetic factors may also play a role. [4]

LCH can occur in individuals of all ages, though it most commonly presents between 1 and 3 years of age. Cases reported in newborns as well as in adults up to their 90s. In children aged 5 to 15, the disease often appears as a solitary bone lesion. The estimated incidence of LCH is 0.4 per 100,000 in children under 15 years of age, with boys being twice as likely to be affected then girls. In adults, however, the trend is reversed [6].

LCH is categorized based on the extent of involvement into unifocal and multifocal forms [6]. The unifocal variant, generally seen in older children and adults, commonly presents as a solitary bone lesion, frequently involving the skull or vertebrae. [4] Less commonly, it may affect the lymph nodes, skin, or lungs, formerly referred to as eosinophilic granuloma. The multifocal form (previously Hand-Schüller-Christian disease) is more aggressive, affecting infants with multiple bone lesions and soft tissue involvement. The disseminated form (formerly Letterer-Siwe disease) is the most severe, with a poor prognosis, particularly in infants, as it affects multiple organs, including the skin, lymph nodes, gastrointestinal tract, bones, and sometimes the central nervous system. Clinically, this form presents with symptoms such as poor growth, weight loss, fatigue, fever, recurrent respiratory infections, and middle ear infections. Other symptoms vary based on the organs involved. The multisystem variant is further classified into high-risk (involvement of vital organs such as the spleen, lungs, liver, and hematopoietic system) and low-risk (without vital organ involvement) groups. [7]

Early symptoms of LCH frequently include cutaneous changes [4], such as seborrhea-like dermatitis on the scalp and body, erythema, infiltration, and yellow-brown, scaly papules. In rare cases, newborns may develop transient skin lesions or dermatitis with nail dystrophy. The disease commonly affects bones, particularly the skull, jaws, long bones of the upper limbs, ribs, pelvis, and vertebrae. Bone involvement can cause swelling and pain but may also be asymptomatic [6]. Lesions in the orbital wall can lead to exophthalmos, while those in the middle ear may result in hearing loss. Osteolytic lesions in the jaw can lead to soft tissue swelling, jaw fractures, and increased tooth mobility.

The classic multifocal form of Langerhans Cell Histiocytosis (LCH), known as Hand-Schüller-Christian disease, is characterized by a triad of diabetes insipidus, exophthalmos, and lytic bony lesions, commonly affecting the cranium, head, neck, and oral cavity. When the maxilla or mandible is involved due to disease progression, it may present as gingival hyperplasia or ulceration. Bone lesions predominantly involve the skull and mandible rather than the maxilla and often appear as multiple punched-out lesions. Radiographically, these lesions are typically radiolucent and commonly affect the central aspect of the mandible or maxilla. In alveolar lesions progression can lead to the destruction of the lamina dura, surrounding bone, and periodontium resulting in a "floating teeth" appearance along with tooth displacement. Non-infectious bone loss is a hallmark of the disease. The mandible shows significant bone destruction, and calvarial bones of the skull displayed multiple punched-out lesions. When LCH affects the mandible, it often leads to severe alveolar bone resorption, creating the characteristic "floating teeth" appearance. [8]

Radiographic imaging often reveals irregular osteolytic lesions, sometimes with sclerotic margins. Involvement of the bone marrow may lead to pancytopenia, accompanied by hepatosplenomegaly, which indicates a poor prognosis. The pulmonary form of LCH can present with symptoms such as rapid breathing, spontaneous pneumothorax, and, in later stages, emphysema. Additional complications include diabetes insipidus, growth disturbances, and neurological symptoms. [7]

Diagnosing LCH relies on clinical evaluation, imaging studies, and biopsy of affected tissues. Histopathological examination typically reveals infiltrates of Langerhans cells, macrophages, lymphocytes, eosinophils, and giant cells. Langerhans cells are characterized by eosinophilic cytoplasm and irregular, grooved nuclei, often described as a "coffee bean" appearance. Immunohistochemically these cells express CD1a antigen and S100 protein. Ultrastructural analysis using electron microscopy can confirm the presence of Birbeck granules. [7]

Treatment options for LCH include chemotherapy, radiotherapy, and corticosteroids. Surgical removal is the preferred approach for isolated bone lesions. Prognosis is primarily influenced by the extent of organ involvement, particularly the involvement of critical organs. Although patient age plays a relatively minor role in determining outcomes/ prognosis.

This **systematic review involves** a comprehensive analysis of case reports and series spanning the past two decades, focusing on the early and often-overlooked manifestations of Langerhans Cell Histiocytosis (LCH) in the oral cavity and skin. It offers critical insights into the demographic and clinical characteristics of dual involvement, which may serve as valuable diagnostic indicators of underlying systemic disease. By synthesizing patterns across diverse presentations, the review underscores the importance of heightened clinical vigilance and interdisciplinary collaboration. The findings have meaningful implications for clinicians, pathologists, and researchers—facilitating earlier diagnosis, more accurate differential considerations, and improved patient management. This work contributes significantly to the literature by enhancing recognition of rare but clinically important presentations of LCH.

This systematic review has been registered in the International prospective register of systematic review PROSPERO <https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42025639647>

**AIM & OBJECTIVES**

This systematic review aims to conduct review to assess oral and cutaneous involvement in Langerhans Cell Histiocytosis. To assess demographics, clinicopathological features, prognostic factors, and outcomes of oral and cutaneous involvement in Langerhans Cell Histiocytosis by systematically reviewing cases reported in the literature.

**MATERIALS AND METHOD**

Case reports and case series of oral and cutaneous involvement in Langerhans Cell Histiocytosis were retrieved by a systematic search of scientific databases, including PubMed Central (National Library of Medicine), Google Scholar (Google, Mountain View, USA) and COCHRANE CENTRAL with the keywords ‘Cutaneous involvement’, OR ‘oral involvement’ AND ‘Langerhans cell histiocytosis’. Retrieved literature was scanned to identify any cases reported with a name differing from Case reports before the year 2005 were not included for the present review. An independent researcher searched the databases and identified 68 relevant studies. Reference checks of the cases identified were also made to help snowballing or networking of the cases. A table was tabulated regarding author, year of publication, demographic data as age, gender, clinical features, histopathological features, and prognostic outcomes and treatment opted for each of the case reports included.

**PROTOCOL**

• The search protocol is designed based on the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analysis-Protocols) guidelines 2015.

ELIGIBILITY CRITERIA

**Inclusion Criteria** Following articles are included;

1. Case reports, case series and case reports and series with reviews on patients with oral and cutaneous involvement in Langerhans Cell Histiocytosis.

2. Articles published in English

3. Case reports and case series reports between 2005 to December 2024

**Exclusion Criteria** Following articles are excluded:

1. Case reports and case series on patients with oral or cutaneous (separately) involvement in Langerhans Cell Histiocytosis

2. Articles published in other language

3. Abstracts

4. Randomized and nonrandomized clinical trials

5. All studies.

6. Articles with incomplete data.

SEARCH STRATEGY

To find pertinent studies on the demographic, clinical and histological conditions and outcomes of Langerhans cells histiocytosis, a thorough search was undertaken in the Google scholar, PubMed, Cochrane and DOAJ database. The filters were fixed at article type (prospective, retrospective, cross-sectional studies), publication date (January 2005 to December 2024), and the best match option. Controlled vocabulary (MeSH terms in PubMed) and free-text terms in the titles and/or abstracts were used to define the search strategy in the database. The search strategies developed using Boolean operators for PubMed and databases is given below and the “screening process of studies is presented in the form of PRISMA flow-chart (Figure1).

DATA EXTRACTION:

Data extraction was done using the following parameters: Author name and year of publication, study design, demographic data, clinicopathological features, differential diagnosis, treatment and outcome of cases.

**Keywords**

**Primary keywords**

* Paediatric and adult patients diagnosed with Langerhans cell histiocytosis(LCH) (P)
* Langerhans cell histiocytosis (LCH) (E)
* Demographics, clinic-pathological features, prognosis, and patients outcome in Oral and cutaneous involvement (O)

**Secondary keywords**

* Patients diagnosed with Histiocytosis X
* Rare disorder of tissue macrophages
* Eosinophilic granuloma
* Hand-schuller-christian disease
* Mucosal lesions in LCH
* Skin lesions in LCH
* Multiorgan involvement in LCH

**Figure 1: PRISMA Flow chart presenting the screening process**

“Abstracts screened”

**(n=79)**

“Additional records identified through other sources (Google Scholar)”
**(n =1011)**

“Total Titles screened”
**(n =1265)**

“Titles screened for duplicate removal”

**(n= 577)**

“Records identified through database searching (PubMed)**”**
**(n = 254)**

## Eligibility

## Screening

## Identification

## Identification

“Records excluded after review of titles
**(n =688)”**

Excluded- duplicates
**(n =498)**

“Records excluded (n=61) after review of abstracts”
**(n =776)**

“Full texts screened on basis of inclusion and exclusion criteria”

**(n=18)**

“Studies included in qualitative synthesis

(n=11)

or

**11 estimates”**

“Studies excluded after review of full text **(n=7)”**

## Included

**Result**

The present systematic review was conducted to assess the demographics, clinical features and prognostic outcomes with oral and cutaneous involvement in Langerhans cell Histiocytosis. The screening process was undertaken in three steps that included screening of titles followed by screening of abstracts and finally screening of full text for inclusion in the review. The characteristics of the studies included in the systematic review are presented in the below tables.”

**“Table 1- Details of the studies included in the systematic review**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study Id** | **Author** | **Year** | **Study design** | **Sample size** |
|  | Manfredi M et al [10]  | 2005 | Case report | n=1 |
|  | Szymańska J et al [11] | 2009 | Case report | n=1 |
|  | George KT et al [12] | 2013 | Case report | n=1 |
|  | Desai V et al [13] | 2013 | Case report | n=1 |
|  | Merglováa V et al [7] | 2014 | Case report | n=2 |
|  | Gautam B et al [8] | 2017 | Case report | n=1 |
|  | Song H et al [14] | 2017 | Case report | n=1 |
|  | Rocha ternio J et al [15]  | 2019 | Case report | n=2 |
|  | Rizzoli A et al [16] | 2021 | Case report | n=1 |
|  | Shakya R et al [17] | 2023 | Case report | n=1 |
|  | Lavaee FA et al [18] | 2023 | Case report | n=1 |

The table 1 represents 11 studies included in the systematic review as per the pre-defined eligibility criteria. All studies explored assess the demographics, clinical features and prognostic outcomes with oral and cutaneous involvement in Langerhans cell Histiocytosis With respect to publication year, the studies were published from 2005 to 2025 over a period of 20 years. Regarding study design, all the 11 included studies were case reports. The sample size across different studies was 1 patient and a maximum of 2 cases reported in one of the studies.

**Table 2- Details of the study participants, intervention, and comparator of the studies included in the systematic review**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Sr No** | **TITLE** **YEAR** **AUTHORS** | **Population: Age and sex**  | **Exposure (E)** | **Oral features (O)** | **Cutaneous features (O)** | **Systemic involvement**  | **Histopathology**  | **IHC (**CD1a antigen and S100 protein**)** | **Prognosis**  |
|  | LCH WITHOUT BONE involvement2005M MANFREDI et al [10]  | 23/M | Langerhans cell histiocytosis  | Palatal, lingual, & vestibular bilateral ulcerations in molar maxillary & mandibular regions. Submucosal nodules in frontal gums. patient reported **pain, burning sensation, & spontaneous & mechanically induced bleeding** during oral hygiene procedure. | Skin of ear & scalp was involved | Lungs involved | Intense & mixed infiltrate of **eosinophilis, histiocytes, & chronic inflammatory elements** among which cells with abundant cytoplasm & reniform nucleus were present. These cells organized in **sheets, groups, / single elements**. | + ve  | No Follow up |
| 2. | LANGERHANS CELL HISTIOCYTOSIS IN A 3-YEAR-OLD GIRL: A CASE REPORT AND LITERATURE REVIEW2009JOANNA DUDA-SZYMAŃSKA, AGNIESZKA WIERZCHNIEWSKA-ŁAWSKA[11] | 3 year /F | Langerhans cell histiocytosis | **ulceration; fibrinous inflammation** in oral cavity. | Multiple **petechiae** on skin & serous membranes | generalized lymphadenopathy, hepatosplenomegaly, various blood abnormalities (anemia, hypoplastic lymphoid cell line, increased serum calcium level), heart hypertrophy, recurrent upper respiratory tract and lung infections. | lymphatic periportal inflammatory infiltrates in liver | **CD1a** cells of lymph node +ve  | No follow up |
| 3. | Langerhans Cell Histiocytosis: An Illusion of Hope 2013Vela D Desai, Smita R Priyadarshinni, Beena Varma, Rajeev Sharma[13] | 4-year-old male | Langerhans cell histiocytosis | floor of mouth showed **greenish yellow pseudomembrane** obscuring alveolar ridge and labial vestibule, loose teeth, **hyperplasia** of gingiva in relation to 41, palate showed similar lesion with **hyperplasia of palatal gingiva - scrappable and tender** on palpation. Periodontal status **- poor with mobility & recession** in maxillary centrals & mandibular canines. | Skin showed multiple **papules on chest,** upper abdomen and right thigh measuring 0.1 × 0.1 mm in size. Hairs -**thin, spare and golden** brown in color and **no seborrheic dermatitis** was present. **Nails showed horizontal brown** line near nail bed. | normal cells with **numerous eosinophils and histiocytes** and numerous chronic **inflammatory cells and candidal hyphae**. |  LCH with multiorgan involvement was given along with anemia and superimposed candidiasis | Not done | did not respond to treatment & succumbed to death after 10 days of his first visit who reported in a terminal stage of LCH with multiorgan involvement |
| 4. | Multisystem Langerhans cell histiocytosis presenting as an oral lesion2013Kallarakkal Thomas George, Ramanathan Anand, Sockalingam Ganasalingam, Zain Rosnah [12] | 8 months / F | Multisystem Langerhans cell histiocytosis | **Ulcerative growth** On hard palate. noticed an erupting tooth in anterior part of upper gums at 3 months old age. Noted **small ulcerated swelling** in same region about 3 months ago. **ulceration had a raised** edge. | occasional mild rashes on the scalp and trunk. | NO | ulcerated hyperplastic parakeratinized stratified squamous epithelium with moderately collagenous connective tissue stroma that was diffusely infiltrated with pale staining cells resembling **histiocytes. lesional cells had an indistinct eosinophilic cytoplasm** and exhibited indentation of nuclei. Varying numbers of **eosinophils, lymphocytes and plasma cells** were interspersed among lesional cells. Abundant **hemorrhagic foci** were evident. **Odontogenic epithelial cells, dentine and enamel matrix** were also present |  + ve | Despite the treatment plan adopted, the baby succumbed to her disease within 6 months after the initial diagnosis |
| 5. | Langerhans cell histiocytosis in childhood Review, symptoms in the oral cavity, differential diagnosis and report of two cases 2014Vlasta Merglováa, Daniel Hrusákb,\*, Ludmila Boudovác, Petr Mukensnablc, Eva Valentováa, Lubor Hosticka[7] | Case 1 - 13 months / FCase 2- 5 months / M | Langerhans cell histiocytosis | erupted molars excessive mobility. surrounding gingiva & mucosa were **swollen, ulcerated**, especially in palatal region, interdental papillae were **necrotic & deep periodontal** pockets were present. | Erythema & papoulopustulae appeared. found reddish, slightly infiltrated skin with numerous, firmly adherent **plaques** on abdomen, hypogastrium & both groins. **dermatitis** was also found in axillae, neck & around auricles. Changes in skin of scalp were similar to **seborrhoeic** dermatitis. Found infiltration of sub **cuticular** tissues in occipital region of around 5 X 5 cm | Oral (bones palate & temporal, mastoid, orbit) & skin  | Parakeratotic pavement epithelium which was ulcerated in places, & subepithelial penetration of connective tissue by polymorphic neoplastic infiltrate consisting mostly of typical **Langerhans cells, with noticeable clusters of eosinophills and histiocytes**.  | positive | Case1 - Eight years after first diagnosis and treatment, child is without symptoms of LCH and degree of bone changes showed no major progression. There are no apparent skin / oral mucosa pathological changes. |
| 6. | Langerhans cell histiocytosis a case report and review2017DR Bhawna Gautam et al[8] |  5 years/ M | Langerhans cell histiocytosis | Lesion in mandible 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. |  **Diffuse, mild swelling** on left lower third of face with overlying **erythematous** surface.Skin lesions since 1 year | NO  |  Langerhans cells are round / oval in shape, with vesicular nucleus, moderate quantity of **eosinophilic cytoplasm & laminated** / dispersed distribution. Abundant eosinophils & other inflammatory cells such as lymphocytes & mononuclear phagocytes may be found accompanying these cells | positive | Undergoing treatment.  |
| 7. | A 12-Month-Old Healthy Girl with a New Oral Ulcer and Chronic Diaper Rash2017 Hannah Song, Johanna S. Song, Elizabeth B. Wallace, Leonard B. Kaban, Mary S. Huang, Stefan Kraft, Martin C. Mihm Jr., Daniela Kroshinsky[14] |  12 months / F | Langerhans cell histiocytosis | 1.5-cm **ulcerated lesion** involving left palatal mucosa.  | thick, greasy, yellow **adherent crust** on temporal scalp, behind ears. **multiple erythematous to violaceous nonblanching papules** with a central **hemorrhagic crust** and surrounding petechiae present on skin of lower right abdomen | **Non healing oral ulcer** & chronic diaper **rash.** erythematous papule on right lower quadrant abdominal skin | submucosal monomorphic infiltrate composed of **epithelioid cells with grooved, “coffee bean-shaped” nuclei.** right lower quadrant abdominal skin also showed superficial dermal and focally cells with **admixed eosinophils intraepidermal infiltrate of epithelioid** | positive -CD1a, S100, and **langerin (CD207)** and **weakly positive for BRAFVE1**. Molecular studies of abdominal skin biopsy confirmed presence of BRAFV600E mutation | patient has completed 6 months of combination therapy with interval improvement in both intraoral mass and cutaneous eruption. |
| 8. | Oral and cutaneous manifestation of lch 2 cases 2019Jefferson da rocha ternio et al [15] | 67 YEARS / F | Langerhans cell histiocytosis | **Granulomatous ulcerative** lesions in hard palate, in right upper gingiva & in right lower alveolar ridge, with important **periodontal compromise** in first right mandibular molar. | Multiple infected **papules throughout skin,** mainly in face, with an aesthetic compromise. Patient reported, skin lesions about 6 months after lesions in mouth and they worsened in number  | On PET- scan Involved bones upper limb, epiglottis. involvement of several anatomical sites, including: cutaneous & subcutaneous lesions on head, neck & upper limb, bone involvement of left preauricular region & involvement of epiglottis. | Proliferation of **histiocytes** that had well-defined cell **boundaries with fine clear intercytoplasmic projections, pale eosinophilic cytoplasm, and vesicle nuclei**. In addition, it was observed presence of **eosinophils permeating**.  | **CDla and S-100 and CD 207 +ve**  | Currently, patient started systemic chemotherapy with prednisolone (80 mg/day) and thalidomide (100 mg/day). |
| 9. | Congenital self-healing reticulohistiocytosis in a newborn: unusual oral and cutaneous manifestations2021Alessandra Rizzoli, Simona Giancristoforo , Cristina Haass, Rita De Vito, Stefania Gaspari, Eleonora Scapillati, Andrea Diociaiuti and May El Hachem[16] | Neonate/ M | Congenital self-healing reticulohistiocytosis | small **erosions were present on tongue** | at birth **multiple polymorphic cutaneous** manifestations on trunk, limbs, & head: **vesicles, blisters, pustules, erythematous and exudative** lesions. | NO  | Dense infiltrate of large histiocytic cells, with **pale cytoplasm and reniform nucleus, filling papillary dermis** and infiltrating epidermis  | Positive for CD1a, Langherin (CD207), S100 protein and e-cadherin. **BRAF V600E mutation** identified both with IHC and PCR | At 2 months of age, all lesions disappeared, with some residual scars. At 5 months follow-up patient is healthy |
| 10. | A case report of adult Langerhans cell histiocytosis and review of the literature 2023Fatemeh Lavaee, Ali Dehghani Nazhvani, Aylar Afshari[18] | 35-year-old man | Langerhans cell histiocytosis | Complaint of **mobile tooth**, first recognized 6 months before his appointment, in right posterior area of mandible. history of extracted mandibular 2nd molar due to mobility | Complained of skin **pruritus with rashes** on several parts of his body (especially his legs, skin rashes were **erythematous crusted macules.** | No  | Para-keratinized stratified squamous epithelium with **exocytosis & intracellular edema**. connective tissue demonstrated diffused & severe infiltration of **chronic inflammatory cells with sheets of histiocytes & numerous scattered eosinophils**. Hemorrhaging areas, **Russell bodies, bacterial colonies**, & focal area of giant cells were also seen. | positive -CD1a, **CD68**, S100, and **Ki**-**67** (in 10% of cells) | Patient was under treatment with prednisolone for 45 days. patient's follow-up (after 45 days) are as follows: his teeth showed less mobility in comparison to last check-up, rashes & skin pruritus lowered. Patient will start chemotherapy for treatment & will be under supervision for complete management. |
| 11. | LANGERHANS CELL HISTIOCYTOSIS IN A PEDIATRIC PATIENT: A TYPICAL PRESENTATION WITH ORAL MANIFESTATIONS2023Royasa Shakya , Bandana Koirala , Ashok Dongol, Iccha Maharjan, Shashi Keshwar, Neetu Jain, and Ashish Shrestha[17] | 5 Years / M | Langerhans cell histiocytosis | **multiple ulcerations were present bilaterally** on hard palate, extending posteriorly - 1.5 X 1 cm x 2 in maximum dimension. After 6 weeks, ulcer showed central area of **creamish white slough of variable thickness with erythematous** periphery. **Grade III mobility** was present teeth 74 and 84 with gingival recession | swelling and structural **distortion in fingernails. blackish discoloration** and destruction of nail plate of middle and little finger of right hand and all fingers of left hand.  | watery discharge was seen from left EAR  | highly cellular connective tissue stroma with numerous scattered **round to polygonal shaped cells with pale cytoplasm** was evident. characteristic **coffee bean shaped and oval nuclei which were folded / indented** with some cells having grooved nuclei were observed. Background stroma was abundant with eosinophils. Overlying epithelium was para to non-keratinized stratified squamous type with irregular rete ridges. | positivity -**CD1a, Langerin (CD-207), and S-100** | lesions have healed and no new lesions have developed in 1 year follow-up visit |

All the search was limited to articles in English language and those published from the year 2005- 2025 were included. Langerhans cell histiocytosis had bimodal distribution; affecting paediatric as well as adult population. The age of the study participants across the studies varied from as less as neonate, 5 months to a maximum of 67 years. The middle aged population had a mean age around 35.21 (4.51) years. Of the 11 studied included, there were 13 cases reported across all case reports. About 7 (53.84%) cases were found in males. Whereas 6 (46.15%) were found in females. The most common affected site of Langerhans cell histiocytosis was skin and oral cavity. In oral cavity, Granulomatous ulcerative lesions in hard palate, in gingiva and in lower alveolar ridge, with involvement of mandibular molars were common. The tumours ranged from 1.5-2 cm in case of oral lesions and about 1.0 cm in the smallest dimension; whereas the cutaneous lesions ranged from as small as 0.5 cm whilst the greatest dimension reported was 5 x 5 cm. In some cases, this clinical information was limited. Duration of presence of lesion varied from 2 months to almost a year. In majority of the cases, it was 5-6 months. Common Clinical presentations of Langerhans cell histiocytosis showed oral features revealed eexcessive mobility of teeth, surrounding gingiva & mucosa swollen, ulcerated, especially in palatal region, interdental papillae were necrotic and deep periodontal pockets were present. Erythema & papoulo-pustulae appeared. Cutaneous features showed reddish, slightly infiltrated skin with numerous, firmly adherent plaques on abdomen, hypogastrium, & both groins; whereas dermatitis was also found in axillae, on neck & around auricles. In majority of the studies there was systematic involvement of lungs, liver, lymph nodes, etc. The Histopathology showed intense and mixed infiltrate of eosinophilis, histiocytes, & chronic inflammatory elements among which cells with abundant cytoplasm & reniform nucleus were present. These cells, mainly organized in sheets, groups, or single elements. The IHC results were positive for CD1a antigen and S100 protein The most common treatment given was with prednisolone and thalidomide and then chemotherapy for complete management.

In this present review out of 13 cases of Langerhans cell histiocytosis, majority of the cases reported for follow-up (11); but in 2 cases; there was no follow-up taken. One case was still undergoing treatment; so the follow-up wasn’t taken. The survival rate across 11 cases (84%) was fair; with only 2 cases who succumbed to death (16%). The follow-up period ranged from 1 month to almost 1 year. In 11 cases; the patient outcome was fair and they did not report recurrence and relapse with absence of muco-cutaneous lesions.

**ASSESSMENT OF RISK OF BIAS**

Risk of bias assessment of all the included studies was performed. All the included studies were case reports; about 2 studies included 2 cases. For the risk of bias assessment of included case reports, JBI’s appraisal tool was used.

**Risk of Bias assessment for Case reports**

JBI critical appraisal checklist for Case reports was used to assess Risk of bias of included case reports (Table 3). The below table shows the critical appraisal of the case reports included in the review. It has been found that most of the case reports included showed all of the items of appraisal with a “yes” response across all the studies; except for in 1 or 2 studies wherein the takeaway message was not mentioned properly or the post treatment condition was not discussed properly. Thus, when the overall quality assessment or Risk of bias is done; it can be interpreted that all of the included case reports showed better quality of assessment.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Author**  | **Were patient’s demographic characteristics clearly described?** | **Was the patient’s history clearly described and presented as a timeline** | **Was the current clinical condition of the patient on presentation clearly described?** | **Were diagnostic tests or assessment methods and the results clearly described?** | **Was the intervention(s) or treatment procedure(s) clearly described?** | **Was the post-intervention clinical condition clearly described?**  | **Were adverse events (harms) or unanticipated events identified and described?** | **Does the case report provide takeaway lessons?** |
| **1** | Manfredi M et al [10]  | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **2** | Szymańska J et al [11] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **3** | George KT et al [12] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **4** | Desai V et al [13] | Yes | Yes | Yes | Yes | Yes | NO | Yes | Yes |
| **5** | Merglováa V et al [7] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **6** | Gautam B et al [8] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **7** | Song H et al [14] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| **8** | Rocha ternio J et al [15]  | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **9** | Rizzoli A et al [16] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **10** | Shakya R et al [17] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **11** | Lavaee FA et al [18] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 3. Critical appraisal of Case reports (JBI appraisal tool)**

**DISCUSSION**

Term Langerhans Cell Histiocytosis (LCH)was officially adopted in 1985 during the Philadelphia Workshop to unify various conditions that were previously grouped under Histiocytosis X. These include eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe syndrome.

The origins of LCH date back to 1893, when Alfred Hand, a young physician at The Children’s Hospital in Philadelphia, documented a case of a 3-year-old child with exophthalmos, polyuria, and tuberculosis. During the autopsy, he observed a distinctive yellow lesion in the skull. In 1915 and 1919, Arthur Schüller and Henry Christian described similar cases, although detailed pathological descriptions only emerged in 1925 through the work of Thompson, Keegan, and Dunn. In 1924, Erich Letterer identified a condition termed aleukemic reticulosis in a 6-month-old infant with fever, purulent otitis media, hepatosplenomegaly, lymphadenopathy, and purpura. A decade later, Siwe expanded on this by describing a similar disease—later termed Letterer-Siwe disease by Abt and Denenholz in 1936. In 1940, Lichtenstein and Jaffe introduced eosinophilic granulomaas another distinct clinical entity, characterized by solitary bone lesions. By 1953, Lichtenstein proposed the broader term Histiocytosis X, with ‘X’ denoting the unknown cause of the condition. The 1985 Philadelphia Workshop refined this classification & introduced the term Langerhans Cell Histiocytosis (LCH) to distinguish it from other histiocytic disorders. Today LCH is now characterized by the presence of T₄ surface antigens, S-100 intracellular protein markers, and Birbeck granules—distinctive rod-shaped organelles observable through electron microscopy.  [9]

LCH is marked by the abnormal proliferation of Langerhans cells, a type of immune cell closely related to macrophages and classified as part of the mononuclear phagocyte system. These lesions primarily affect organs where Langerhans cells normally reside such as the skin, bone marrow, lymph nodes, spleen, liver, lungs, pleura, and central nervous system. The exact prevalence of LCH remains unclear, epidemiological data from in the United States estimates an incidence rate of approximately 0.5 cases per 100,000 children annually. The disease can manifest as either unisystem (affecting a single organ system) or multisystem (involving multiple organ systems).

Although the pathogenesis of LCH remains unclear, recent studies suggest an immune system dysfunction may play a potential role. Patients with LCH often exhibit a deficiency of circulating suppressor T lymphocytes (T₈) and an increased ratio of helper (T₄) to suppressor (T₈) cells. Additionally, histological abnormalities in the thymus have been noted in some cases. Experimental treatments using calf thymus extract (thymosin) have shown potential in restoring the T₄: T₈ ratio to normal, though clinical outcomes vary. Spontaneous remission has been associated with a normalized immune cell ratio, supporting the hypothesis that LCH may arise from excessive immune responses triggered by antigenic stimulation and abnormal macrophage activity. [9]





**Figure 2. Activating MAPK Pathway Mutations in Langerhans Cell Histiocytosis (LCH)**

Recent advances in molecular and cellular research have fundamentally reshaped the understanding of LCH, shifting it from a disorder of immune dysregulation or transformed epidermal Langerhans cells (eLCs) to a myeloid neoplastic disease. Historically, due to shared histologic features and expression of surface markers such as CD1a and CD207 (langerin), LCH cells were thought to be either reactive immune cells or transformed eLCs. However, more recent gene expression studies have revealed that LCH cells, particularly CD207+ cells found in lesions, are markedly less differentiated than normal Langherhan Cells. These findings suggest that LCH cells likely originate from early myeloid progenitors rather than from mature epidermal dendritic cells. [20]

A key breakthrough in understanding LCH pathogenesis occurred in 2010, when researchers identified recurrent somatic BRAFV600E mutations in over 50% of LCH lesions. [19] This mutation results in the constitutive activation of the MAPK signaling pathway, a pathway often implicated in oncogenesis. Following this discovery, other mutations affecting the MAPK pathway—such as those in the MAP2K1 gene (encoding MEK1) and other BRAF mutations, including fusions and indels—have been documented. Collectively, approximately 85% of LCH lesions have been found to harbor activating mutations in components of the MAPK pathway, reinforcing the concept that LCH is a clonal neoplastic disorder driven by MAPK dysregulation.

Further supporting for this model comes from studies utilizing high-sensitivity PCR assays which have detected BRAFV600E mutations in hematopoietic stem and progenitor cells (HSPCs) from bone marrow aspirates and peripheral blood myeloid precursors in patients with disseminated LCH. Importantly, this mutation was not detected in peripheral blood mononuclear cells from patients with single BRAFV600E+ LCH lesions, suggesting that the extent and dissemination of LCH are influenced by the developmental stage of the myeloid cell in which the mutation arises. Song H et al [14] reported weak positivity for BRAFVE1. Molecular studies of abdominal skin biopsy confirmed presence of BRAFV600E mutation. [14]

Mouse model experiments have provided additional insight into the disease’s biology. When BRAFV600E is expressed in langerin+ cells, mice develop localized, mild LCH-like lesions with little systemic impact. In contrast, expression of BRAFV600E in CD11c+ myeloid progenitor cells leads to aggressive, multisystem disease with involvement of organ such as in the liver, lung, spleen, and bone marrow—mirroring high-risk human LCH. This indicates that the earlier in myeloid differentiation the MAPK-activating mutation occurs, the more severe and widespread the disease.

Moreover, pathologic MAPK activation in LCH lesions results in cellular dysfunction. By upregulating anti-apoptotic proteins like Bcl-xL and downregulating CCR7, a chemokine receptor involved in cell migration. These alterations trap LCH cells in tissue lesions, preventing them from migrating to lymph nodes thereby contributing to persistent lesion and disease pathology. [20] Altogether, these discoveries support a modern framework of LCH as a clonal, myeloid neoplasm rooted in misguided myeloid differentiation. According to this model, the timing and lineage context of MAPK pathway mutation determine the phenotype and clinical behavior of LCH, offering not only a clearer pathologic understanding but also potential therapeutic targets for intervention.

This systematic review provides a comprehensive analysis of 11 case reports encompassing 13 patients diagnosed with LCH, with a focus on oral, cutaneous, and systemic manifestations. The findings reaffirm the clinical heterogeneity of LCH, underscoring the diagnostic and therapeutic challenges associated with this rare disease.

LCH affects a wide age spectrum, with a **bimodal age distribution** observed in this review, ranging from 5 months to 67 years. This aligns with existing literature suggesting peaks in early childhood and middle adulthood. [21] The adult subgroup demonstrated a mean age of approximately 35 years, comparable to prior studies emphasizing the relevance of LCH as a differential diagnosis in young to middle-aged adults [19]. In this systematic review Jefferson da rocha ternio et al 2019 [15] reported a case with the highest age i.e 67 years old with the LCH and the youngest begin neonate reported by Alessandra Rizzoli et al 2021. [16] A **slight male predominance (53.84%)** was observed, which is consistent with previous epidemiological data suggesting that LCH has a male-to-female ratio ranging from 1.2:1 to 2:1 [22]. Although gender does not appear to significantly influence prognosis, awareness of this trend is helpful in clinical suspicion and assessment.

The most **commonly involved anatomical sites** in our review were the **oral cavity and skin**. Oral lesions showing predilection for the **hard palate, gingiva**, and **mandibular alveolar ridge**—commonly presenting as ulcerative, granulomatous lesions with periodontal involvement. These findings are supported by past reports indicating that oral involvement may mimic aggressive periodontitis or osteomyelitis [23] [24]. Clinicians should remain vigilant for persistent or atypical oral lesions, especially when accompanied by systemic signs. Oral involvement in Langerhans Cell Histiocytosis (LCH) may be among the earliest clinical manifestations of the disease, positioning general dentists as key players in its early detection and diagnosis. Oral lesions may appear as solitary or multiple areas with irregular surface morphology, often leading to mucosal ulceration. These can occur with or without underlying bone involvement. Gingival lesions in LCH frequently present with bleeding, gingival recession, and are typically associated with loss of periodontal attachment and increased tooth mobility. In severe cases, spontaneous dental avulsion, highlighting the destructive potential of the LCH within the oral cavity

Cutaneous manifestations such as **erythematous, infiltrated plaques** and **dermatitis** in areas like the groin, axillae, and neck were also prominent. These lesions are often misdiagnosed as eczema or candidiasis, delaying appropriate management as suggested by Haupt et al., (2013). Similarly, systemic involvement, especially of the **lungs, liver, and lymph nodes**, was noted in a significant number of cases, emphasizing the **multisystemic nature** of LCH and the importance of thorough diagnostic imaging and laboratory evaluations (26). For instance, Rocha ternio J et al [15] presented a case with multiple coalescent papules scattered across the body, predominantly on the face, resulting in noticeable aesthetic impairment. These cutaneous manifestations, alone are not predictive of disease outcome and not used in classifying the condition as either single-system or multisystem LCH, they are clinically significant. In many cases, the skin lesions emerged following the onset of oral lesions and progressed in parallel with the worsening of the oral condition was reported by Jefferson da rocha ternio et al 2019. [15] This prompted dermatological consultation, reinforcing suspicion of LCH. The diagnosis of the cutaneous lesions was ultimately supported by the patient’s overall clinical presentation, particularly the progression and association with oral findings.

###  **Why do Oral and Cutaneous lesions occur Simultaneous in LCH?**

### Langerhans cells are **specialized antigen-presenting dendritic cells** found in both the **epidermis of the skin** and the **oral mucosa**, particularly in the **gingival epithelium**. As LCH is a **clonal disorder involving uncontrolled proliferation** of these cells, any tissue that naturally harbors Langerhans cells including **skin, oral mucosa, bone, lungs, liver**, and **lymph nodes**. LCH can be either **localized** or **multisystemic**. [21] In **multisystem LCH**, multiple tissues are often involved **simultaneously** due to **hematogenous spread** or **multifocal activation** of pathological Langerhans cells. Both skin and oral mucosa arise from **ectodermal origin** and share a similar immune surveillance environment. This makes them susceptible to **simultaneous infiltration** as a pathological Langerhans cells often proliferate systemically, showing **tropism (affinity)** for **epithelial-rich and inflamed sites**, which are frequently seen in both **periodontal tissues** (gingiva, alveolar bone) and **skin** (axillae, groin, trunk). [21] Inflammation in these areas may promote **local proliferation** or **homing** of LCH cells via **chemokines like CCR6, CCR7**. Genetic mutations (like **BRAF^V600E**) result in **constitutive activation** of the MAPK/ERK pathway. This leads to **persistent survival signals** and uncontrolled proliferation of LCH cells, allowing **dissemination to multiple organs**, including **cutaneous and oral sites**. [19]

**Histopathologically**, LCH is characterized by infiltration of **Langerhans cells with reniform nuclei** accompanied by **eosinophils and chronic inflammatory cells**, as observed in all reviewed cases. **Immunohistochemical positivity for CD1a and S100 proteins** confirming the diagnosis. These marker are standard distinguishing LCH from other histiocytic disorders. [27] Under light microscopy, Langerhans cells can be identified in the epidermis. These cells typically have a kidney-shaped or grooved nucleus, often described as resembling coffee beans due to the longitudinal nuclear groove. [22] The surrounding inflammatory infiltrate which includes eosinophils, and the Langerhans cells appear round in morphology. The gold standard for confirming the diagnosis of LCH is the identification of Birbeck granules, these are rod- or tennis racket-shaped organelles unique to Langerhans cells (via electron microscopy). However, this method is rarely used in routine clinical settings. The distribution density of Birbeck granules may vary depending on the tissue type and the extent of disease involvement. [30] Immunohistochemically, Langerhans cells in LCH are positive for S100 protein and CD1a, which are classic diagnostic markers. Langerin (CD207), a C-type lectin and a newer monoclonal marker, has a higher specificity than CD1a in detecting Langerhans cells and is directly involved in the formation of Birbeck granules. [30] Song H et al, [14] Rocha ternio J et al, [15] Rizzoli A et al, [16] Shakya R et al, [17] Lavaee FA et al [18] has reported langerin positive in IHC. Langerin expression can also be identified using electron microscopy, further confirming the presence of Langerhans cells. Additional immunophenotypic markers like Vimentin, CD45, and ecto-ATPase can be used to support diagnosis, as these are involved in cellular structural integrity and membrane-associated functions. [31]

In terms of **treatment**, corticosteroids (notably **prednisolone**) and **thalidomide** were the most frequently used agents, followed by **chemotherapy** in more aggressive or refractory cases. This therapeutic approach reflects current treatment guidelines for LCH, which recommend tailored regimens depending on disease extent and risk organ involvement. [28]

Patient outcomes in this review were generally favorable, with **84% survival** and minimal recurrence among those with adequate follow-up. These results are reassuring and underscore the importance of early diagnosis and consistent follow-up in improving prognosis. However, two patients (16%) succumbed to the disease in cases reported by George KT et al [12], Desai V et al. [13] Minkov M et al. (2002) reported that **LCH can be fatal**, especially in cases with multisystem involvement or delayed diagnosis. [29]

Despite the limited sample size and inherent variability inherent in case report data, this review highlights the **diverse clinical presentation**, **importance of histological confirmation**, and **effective treatment outcomes** in LCH. It reinforces the role of **interdisciplinary collaboration** among dentists, dermatologists, pathologists, and oncologists in ensuring early detection and management.

**CONCULSION**

LCH remains a diagnostic challenge due to its diverse presentation across multiple organ systems. Oral and cutaneous manifestations, though frequently overlooked, can serve as early indicators and significantly aid in timely diagnosis. The conclusion appropriately highlights the diagnostic significance of oral and skin manifestations in Langerhans Cell Histiocytosis (LCH). To further enhance its impact, this systematic review emphasizes the necessity of early recognition of these signs as potential indicators of systemic involvement. Prompt referral to specialties such as oncology, dermatology, or oral pathology is recommended for comprehensive evaluation. Additionally, interdisciplinary collaboration among dental professionals, dermatologists, pediatricians, and hematologists is crucial for timely diagnosis, accurate staging, and effective management of LCH, ultimately improving patient outcomes.

**LIMITATIONS**

This review is constrained by the small number of cases, inconsistent reporting across case studies, and incomplete follow-up data in some reports. Additionally, as only English-language literature was included, there is a possibility of language bias.

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