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**Dr. Rekha P Radhakrishnan**
Assistant Professor, Department of Periodontics, Govt Dental College, Kottayam, Kerala, India

**Dr. Lekshmi A Jayasree**
Senior Lecturer, Department of Periodontics, Mar Baselios Dental College, Kothamangalam, Kerala, India

**Dr. Shibu Godfrey Periera**
Professor and H.O.D, Department of Periodontics, Govt Dental College, Thrissur, Kerala, India

**Dr. Divya P Vishalakshi**
Associate Professor, Department of Periodontics. Govt Dental College, Thiruvananthapuram, Kerala, India

**Dr. Susanna S Brainerd**
Consultant Periodontist, Pune, Maharashtra, India

**Corresponding Author:**
**Dr. Lekshmi A Jayasree**
Senior Lecturer, Department of Periodontics, Mar Baselios Dental College, Kothamangalam, Kerala, India

# Langerhans cell histiocytos-a diagnostic dilemma to the dentist? Review with a rare case report

**Dr. Rekha P Radhakrishnan, Dr. Lekshmi A Jayasree, Dr. Shibu Godfrey Periera, Dr. Divya P Vishalakshi and Dr. Susanna S Brainerd**

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**Abstract**
The diagnosis and management of severe periodontitis in young individuals is often challenging. Oral and periodontal manifestation may be the first sign of underlying systemic diseases and careful multidisciplinary approach in diagnosis and management is of great importance for a better overall outcome. Gingival biopsy is a mandatory simple and reliable investigation to rule out systemic causes when severe periodontal destruction noted in young.
In this case report, we present a young adult male who presented with severe periodontitis, which showed poor response to conventional periodontal treatment, later confirmed as Langerhans cell histiocytosis, a rare neoplastic disorder.

**Keywords:** Periodontitis, Alveolar Bone loss, Rare diseases, Histiocytes, Histiocytosis-Langerhans cell, Biopsy

## Introduction
Periodontitis is considered as an infectious inflammatory disease of the supporting structures of the teeth, the extent and severity of which is primarily ascribed to the host immune response. Certain systemic conditions, via their ramifications on host immunity may alter the severity of periodontitis or actually simulate severe periodontitis. The diagnosis and management of periodontitis is often demanding, especially in cases where severe destruction of the periodontium is seen in young individuals. An underlying chronic disease or disability with a major impact on immune system can be the root cause of an aggressive form of periodontal disease presenting in children and young adolescents.[1] One such condition seeking the attention of the clinicians is Langerhans cell histiocytosis, listed under "conditions which affect the periodontal apparatus independently of dental plaque/biofilm-induced inflammation" in the 2017 AAP classification of Periodontal diseases. The young male reported here presented with extreme periodontal destruction, refractory to conventional periodontal therapy, and subsequently diagnosed as Langerhans Cell Histiocytosis, a rare neoplastic disorder.

## Clinical Presentation
An 18-year-old male reported to the Department of Periodontics, Government Dental College, Thrissur in January 2021 with the complaint of severe pain of gums and multiple mobile teeth for 2 years. Pain was gradual in onset, intermittent, and non-radiating. Upper right first premolar was lost due to mobility one month before the first visit, for which he consulted a local hospital. Nonsurgical periodontal therapy was done in two different appointments and systemic antibiotics and analgesics were prescribed. Periodontal surgical intervention was advised and root canal treatment 46 was done. But after the non-surgical therapy and endodontic therapy, there was no improvement and patient was referred to the tertiary dental care centre for further treatment. Medical and family history were insignificant.
On general examination patient was healthy and moderately built. Vital signs were within normal limits with a right submandibular lymph node palpable, non-tender, soft in consistency, and movable.

Routine haematological tests were done, results were within normal limits. (Table no 1). Random blood sugar level was towards lower normal blood sugar level. Mild skin eruptions were noted on face.

Intra-oral examination revealed plaque and calculus deposits, severe gingival inflammation, deep periodontal pockets, generalised bleeding on probing and gingival hyperplasia. Severe clinical attachment loss with surface ulcerations and necrosis were noted in relation to [16, 15, 41, 31, 36] with grade III furcation involvement of all posteriors. Panoramic radiographs demonstrated widespread extensive alveolar bone loss, till apical third in relation to multiple teeth [15, 36, 35, 45, 46]. This was consistent with severe teeth mobility clinically seen. Soft tissue and bone destruction were far more poignant than a case of generalized periodontitis and a biopsy was planned to rule out an underlying systemic cause.

Nonsurgical periodontal therapy repeated before biopsy to reduce the inflammatory component. Extraction of 36 was done with gingival and bone biopsy and the specimens were sent for histopathological examination. The mandibular right second premolar was also extracted due to severe mobility and persistent root sensitivity followed by a combination antibiotic therapy. [Amoxicillin 500mg, every 8 hours for 5 days, Metronidazole 400mg, every 8 hours for 5 days].

On histopathological investigation, proliferation of large multinucleate pale staining giant cells with irregular elongated coffee bean nuclei, prominent nuclear groove and folds were noted. This finding was suggestive of Langerhans Cell Histiocytosis. For confirmation immune histochemical staining was performed; the result was positive for CD1a marker which was specific for the disease. Skull radiography was advised and it revealed no abnormalities.

Patient was referred to tertiary medical care centre for further investigation and treatment. MRI, PET scan was done and other risk organ and system involvement was ruled out. Curative chemotherapy with vinblastine, prednisolone started. Currently he is undergoing chemotherapy.

**Discussion**

With a low annual incidence rate, and that too with rarer incidence among adults, Langerhans cell histiocytosis (LCH) is a heterogeneous disease, which is characterized by accumulation of dendritic cells with features similar to epidermal Langerhans cells in various organs [2, 3]. Literature shows a slight male and Caucasian predominance among affected. Along with the abnormal clonal proliferation of immuno phenotypical and functionally immature Langerhans cell, eosinophils, macrophages, lymphocytes, and, occasionally, multinucleated giant cells also proliferate and may infiltrate in to bone, skin, mucosa and other internal organs resulting in their destruction [3-5]. Implicating a neoplastic origin for the disease, somatic mutations in BRAF V600E and MAP2K1 gene have been identified to occur in about 75% of patients. It also shares characteristic features of an abnormal reactive process [5-7]. Epstein Bar virus infection has been suggested as an etiology in number of cases, even though the association could be a chance occurrence [7].

Traditionally based on different clinical manifestation and age Langerhans cell Histiocytosis was categorised into three different types [4, 8].

1. Type I, Eosinophilic granuloma (Chronic focal LCH): Most common and Benign
2. Type II, Hans-Schüller-Christian disease (Chronic disseminated or diffuse LCH), manifesting with peculiar triad of exophthalmos, osteolytic lesions of the cranium and diabetes insipidus.
3. Type III Abt-Letterer-Siwe disease (Acute disseminated LCH), considered as the malignant form of LCH. Generally affecting children under three years old, with a prompt fatal course.

Congenital reticulo histiocytosis (Hashimoto-Pritzker syndrome) is a purely cutaneous benign form of LCH, exclusively affecting the mucosae characterized by the appearance of dark nodules on the trunk, face and scalp which is self-healing [4, 5].

Based on the extent of involvement at the time of diagnosis, Langerhans cell histiocytosis classified clinically into a single-system disease (SS-LCH), affecting a single system which is with a favourable prognosis and a multi-system form (MS-LCH), involving multiple organ systems, especially risk organs, with a poorer prognosis [5]. (Table no 2) Multiple Organ and risk organ involvement in young age may influence the progression and severity of disease. Bone followed by the skin, lymph nodes and lung are mostly involved in single-system LCH. Skeletal lesions of LCH often affect the skull, long bones, pelvis, ribs, vertebra, facial bones and jaws, particularly the posterior regions of the mandible [7].

Lesions of the oral cavity may appear as a red flag sign of Langerhans cell histiocytosis elsewhere in the body, even rarely may be the sole presentation or may occur during the reactivation of the disease [5]. Oral signs and symptoms include odontalgia, sore mouth, gingival inflammation and bleeding, gingival hypertrophy, unpleasant taste, halitosis, mobility of teeth, jaw pain, facial swelling, mental nerve anaesthesia, failure of extracted tooth sockets to heal, mucosal surface ulcerations, necrosis and cervical lymph adenopathies. Loss of supporting alveolar bone with strict periodontal containment of the lesion, could lead to an erroneous diagnosis of aggressive periodontitis, and necrotizing ulcerative periodontitis [9].

The lesion may present with atypical radiographic manifestations in maxilla and mandible which may include solitary intra bony lesions principally in the body or ramus of the mandible, or multiple bone lesions without corticated margins or even with invasive margins. This alveolar bone loss may eventually lead to an appearance of ‘floating teeth’ characterised by circumscribed radiolucent areas around teeth. An intact bony crest with a scooped out alveolar bone lesion below on either mesial or distal side of the bone may aid in differential diagnosis. At times, neo bone formation within bony defects may also help to differentiate it from periodontal disease [4].

Absence of characteristic clinical and radiographic features necessitates the confirmatory diagnosis of LCH based on microscopic examination of the obtained biopsy specimen. The histologic picture reveals histiocytes with abundant eosinophilic cytoplasm and lobulated or coffee bean-like nucleus containing delicate chromatin and inconspicuous nucleoli admixed with variable number of eosinophils, lymphocytes, neutrophils, plasma cells and multinucleated giant cells with elongated, zipper-like cytoplasmic Birbeck granules specifically observed in electron microscopy [10]. Advancements in immunohistochemistry have facilitated the identification of specific immuno histochemical markers, characteristic of LCH which includes expression of CD1a, S100 protein and Langerin (CD207) in Langerhans cells. A definitive LCH diagnosis can be set when a positive staining for CD1a antigen is obtained following the histological and electron microscopy findings [10].

Treatment of the disease depends fundamentally on a careful multidisciplinary evaluation and correct diagnosis. (Table 3) [2] A predetermined protocol for management of LCH being nonexistent, the available treatment alternatives include combinations of surgical removal of localized bone lesions, chemotherapy and radiation. Variegated testimony of results have been obtained with the use of corticosteroids, vinblastine, mercaptopurine, methotrexate, cyclophosphamide, monoclonal anti CD 1a antibodies. Unifocal lesions may resolve spontaneously or can be treated with curettage or intralesional corticosteroid injections. Low dose radiotherapy can be considered if inaccessible to surgical curettage and also in recurrent cases [8].

In the present case, the young male presenting with severe periodontal destruction refractory to nonsurgical therapy along with antimicrobial therapy transpired the suspicion of a systemic cause which in turn lead to a diagnostic biopsy. In the biopsy specimen, presence of an atypical proliferation of Langerhans cells resulted in diagnosis. This was confirmed by immuno histochemistry which was positive for CD1a marker. Since age of the patient was more than 15 years, multi organ involvement needed to be ruled out and this was done by various investigations, including MRI and PET scans. The results were assessed and because of non-contributary findings, prognosis was evaluated as good. Combination chemotherapy with corticosteroids and vinblastine were initiated, advised for one year, which is continuing. Patient was recalled for follow up periodontal evaluation. Although resolution of gingival inflammation, hypertrophy and other clinical signs were noted, teeth were mobile due to extensive alveolar bone loss also causing an inability to maintain optimal oral hygiene. Over all periodontal prognosis assessed was hopeless and extraction of teeth with severe mobility were suggested with wide curettage and rehabilitation later on.

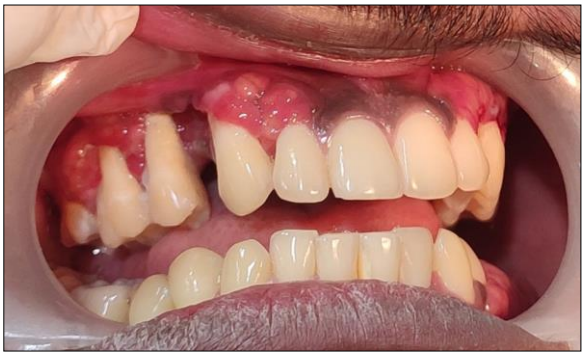

**Fig 1:** Clinical photographs showing severe inflammation, gingival enlargement in relation to maxillary right quadrant

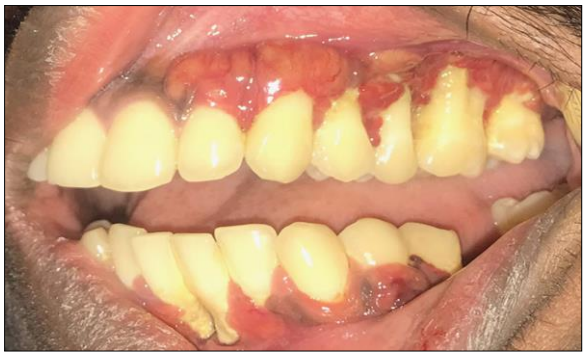

**Fig 2:** Clinical photographs showing severe inflammation, Gingival enlargement in relation to maxillary left quadrant**.**

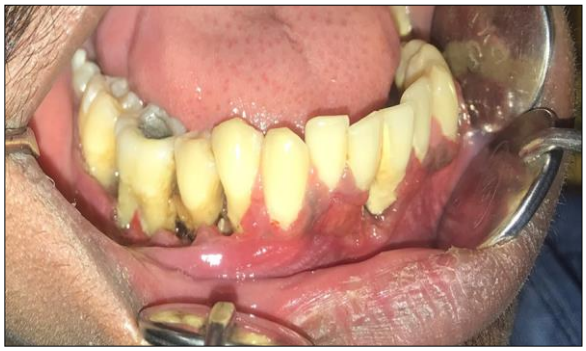

**Fig 3:** Clinical photograph showing severe inflammation, deep pockets and necrosis in relation to mandibular left posteriors

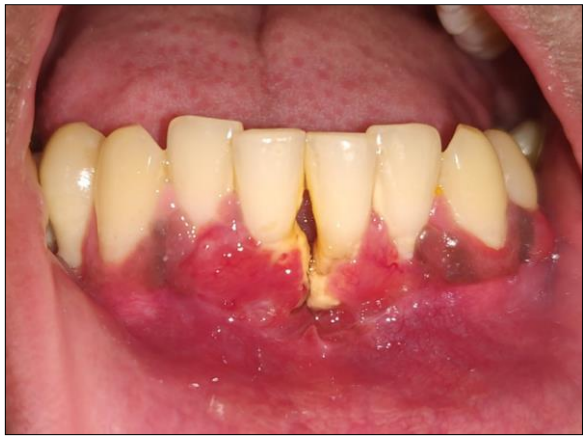

**Fig 4:** Clinical photographs showing severe inflammation, in relation to mandibular anteriors.

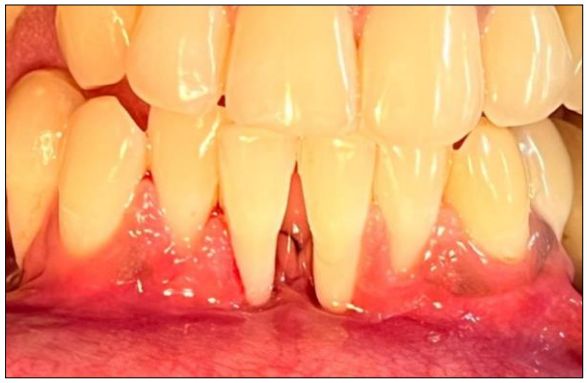

**Fig 5:** clinical photograph showing resolving inflammation in anterior region post 6 months chemotherapy

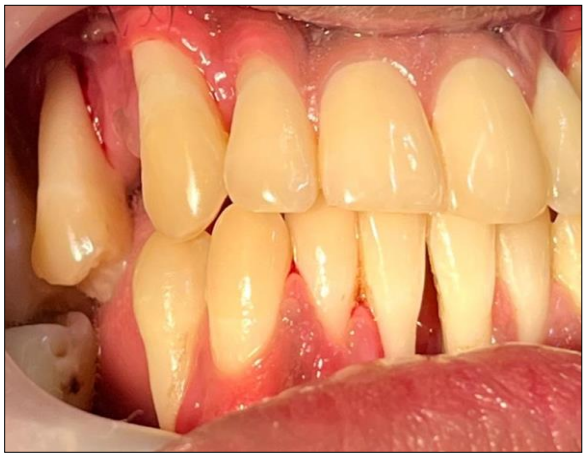

**Fig 6:** Clinical photograph showing resolving inflammation in right quadrant post 6

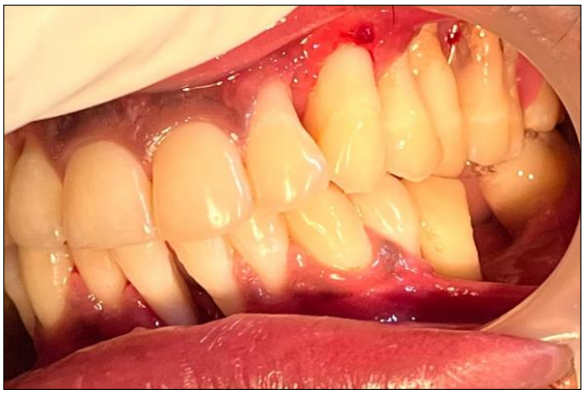

**Fig 7:** Clinical photograph showing resolving inflammation in left quadrant post 6 months chemotherapy

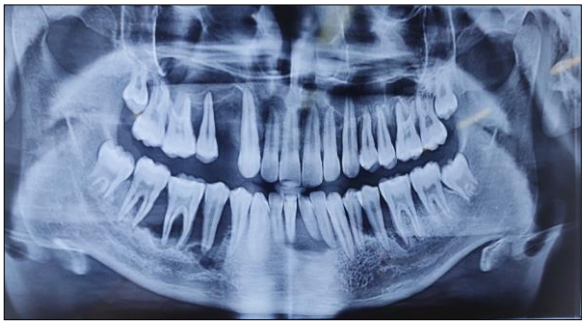

**Fig 8:** Panoramic radiograph showing severe generalized alveolar bone

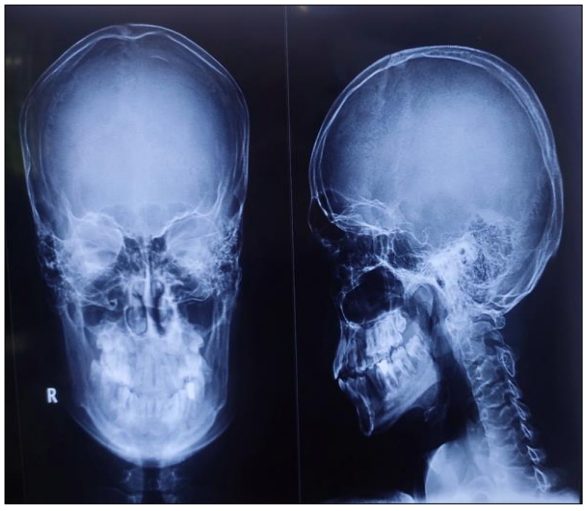


**Fig 9:** Postero anterior and lateral cephalometric views showing no significant abnormalities

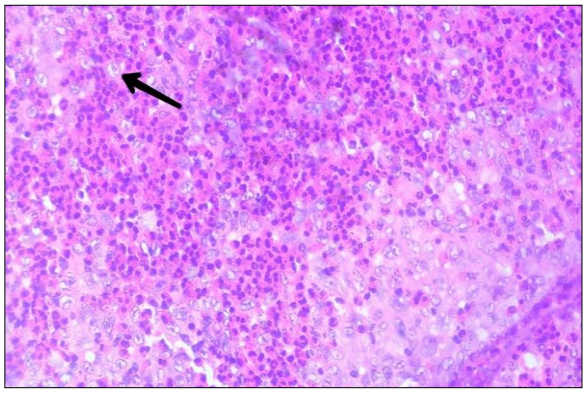

**Fig 10:** Hematoxylin—eosin staining of gingival biopsy specimen. Arrow showing Langerhans cells with coffee bean shaped basophilic nuclei

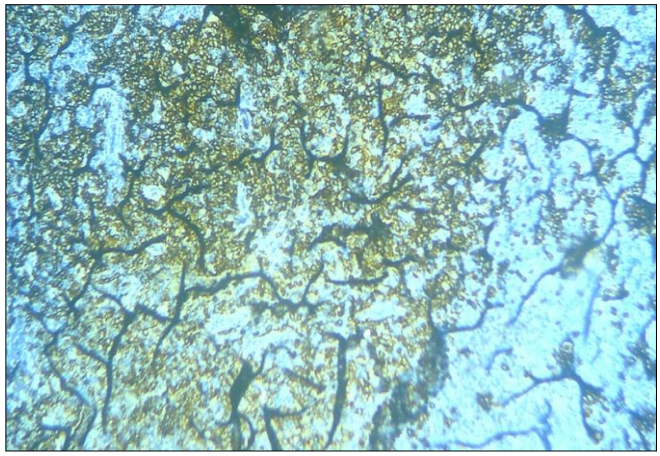

**Fig 11(a):** Immunohistochemical stain for CD1a antigen with strong reactivity (original magnification 10x)

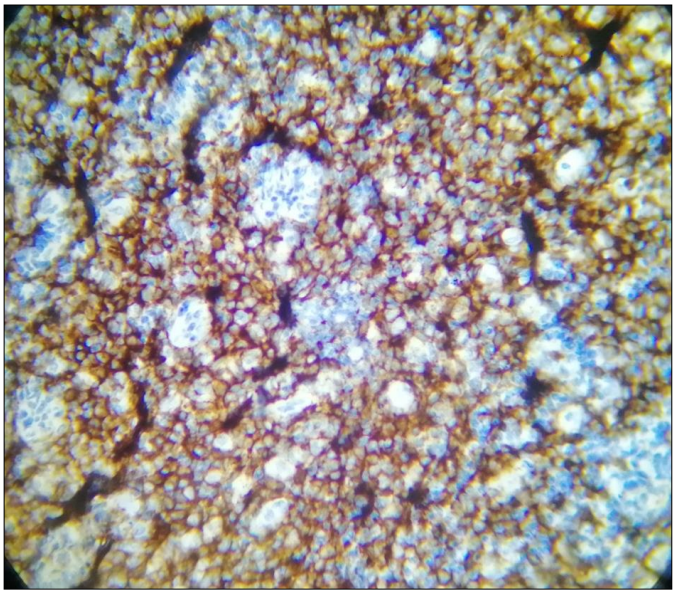

**Fig 11 (b):** Immunohistochemical stain for CD-1a with strong reactivity (original magnification 40x)

| | | |
|---|---|---|
| 1 | Haemoglobin | 15.6 gm% |
| 2 | Total WBC | 9400/ cmm |
| 3 | DLC | P - 76%,L 26%E-04% M-B - |
| 4 | ESR | 06 mms/hr |
| 5 | Platelet count | 3.6L/cmm |
| 6 | Bleeding time | 1 min 30 sec |
| 7 | Clotting time | 5 min |

**Table 1:** Single System LCH (SS-LCH): One organ/system involved

| |
|---|
| (uni- or multifocal):<br>➢ Bone: unifocal (single bone) or multifocal (> 1 bone)<br>➢ Skin<br>➢ Lymph node<br>➢ Hypothalamic-pituitary / Central nervous system<br>➢ Lungs (primary pulmonary LCH)<br>➢ Other (e.g. thyroid, gut) |
| Multisystem LCH (MS-LCH): Two or more organs/systems involved |
| ➢ With involvement of “Risk Organs” (Hematopoietic system, spleen, and/or liver,<br>tumorous CNS)<br>➢ Without involvement of “Risk Organs |

**Table 2:** Laboratory and Radiographic Evaluation for patients with LCH

| |
|---|
| Full blood count |
| Hemoglobin |
| White blood cell and differential count |
| Platelet count |
| Blood chemistry |
| Total protein |
| Albumin |
| Bilirubin |
| ALT (SGPT) |
| AST (SGOT) |
| gGT |
| Creatinine |
| Electrolytes |
| Erythrocyte sedimentation rate (ESR) |
| Abdominal ultrasound (in particular for young children) |
| Size and structure of liver and spleen |
| Abdominal lymph-nodes |
| Coagulation studies |
| INR/PT |
| APTT/PTT |
| Fibrinogen/factor I |
| Chest Radiograph (CXR) |
| Skeletal radiograph surveya, b |
| ALT (SGPT), alanine transaminase (serum glutamic pyruvic transaminase); APTT/PTT, activated partial thromboplastin time/partialthromboplastin time; AST (SGOT), aspartate transaminase (serum glutamic oxaloacetic transaminase); gGT, gamma-glutamyltransferase; INR/PT, international normalized ratio/prothrombin time; MRI, magnetic resonance imaging; PET, positron emission tomography; Tc, technetium. |

## Conclusions

Oral manifestations typically seen for more common diseases like periodontal diseases may occur as initial symptoms in diseases like Langerhans cell histiocytosis. When atypical periodontal destruction and gingival inflammation refractory to conventional therapy is seen, a detailed history should be taken and relevant investigations should be considered. This should be duly followed by a diagnostic biopsy to rule out systemic causes. Rare conditions like Langerhans cell histiocytosis may reflect only in oral cavity or may appear as the primary symptom before revealing itself elsewhere in the body. Dental professionals may be the earliest identifiers to single out these conditions as patients may present themselves primarily to them for relieving their oral health related difficulties. The responsibility is vested upon them to identify and send the patient for early possible interventions.

Due to the unpredictable course and inconsistent nature of presentation of the lesion, optimal treatment of LCH still remains controversial and also, the possibility of recurrence of the condition is apparent both in juvenile and adult cases. After successful resolution, a meticulous dental rehabilitation should be accomplished to improve the quality of life of the patient. An early diagnosis, a multidisciplinary team approach and rehabilitation as well as a close follow up are the mainstay in effective management of this rare condition.

## Conflict of Interest

Not available

## Financial Support

Not available

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