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Case Report

The Diagnostic Conundrum of Oral Langerhans Cell Histiocytosis: Insights from Case Report for Early Identification by the Pediatric Dentist

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Abstract

Oral manifestations of Langerhans cell histiocytosis in the pediatric population are unusual in their presentation, not frequently encountered by dental professionals, often missed or misdiagnosed, and may well be the first or only sign of the disease, which could be fatal in its severe form, thus making it critical that these diagnoses are not misgauged. Due to the rareness of this condition, clinically useful guidelines are unavailable for guiding oral health care professionals. Here, we present two cases: A 2.5-year-old female and an 11-month-old male of Asian origin, both of whom were diagnosed by pediatric dentists via oral manifestations. To minimize delay in diagnosis, an analytic roadmap is also presented to help pediatric dentists and other oral health care professionals diagnose this condition accurately. It will also help physicians from different specialties with an overview of appropriate referrals.

Keywords: Child, dentist, langerhans cell histiocytosis, manifestation, oral, pediatric

Introduction

Unusual clinical presentations such as abnormal and premature mobility of deciduous teeth, gingival erythema, and atypical ulcerations in infancy and early childhood may be encountered by a pediatric dentist in the form of difficulty chewing and painful tooth brushing. Such oral manifestations may often be the first sign of an underlying, sinister systemic disease.

One such condition is Langerhans Cell Histiocytosis (LCH), a rare proliferative histiocytic disorder of unclear etiology that primarily affects children and has a varied presentation, predominantly affecting bone. The diagnosis is often made in childhood; many cases eventually progress into adulthood.

Oral manifestations have been reported in as high as 77% of cases, and in 20% of instances, they may be the first sign of disease and may as well be the only affected site.[1] This makes it particularly important for the pediatric dentist to be able to recognize these signs and symptoms. Furthermore, since the prognosis worsens with the increasing number of organ systems involved, catching the disease early may greatly benefit these patients by affording them a quicker shot at treatment, thus limiting the disease severity.

The present article reports two new cases of LCH diagnosed by pediatric dentists to highlight the importance of their role in diagnosing the condition, providing an ethically approved analytic roadmap focusing on the pediatric age group, and stressing the importance of appropriate referral and a multidisciplinary approach.

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Case 1

A 2.5-year-old female patient reported to our institute's outpatient unit of pediatric dentistry with a chief complaint of pain and bleeding from the upper left maxillary back teeth. A child was average 6–7 months ago when she developed pain while eating, brushing, and food lodgement, which was challenging to clean. A private practitioner consultation was made, and gingival massage ointment was prescribed. A month later, there was increased pain and difficulty eating, and the patient was referred to the tertiary care center. There was no contributing past medical history except that she was hospitalized for 1 day for pneumonia at 6 months, but no scans were available. A child weighing 11.8 kg and 92 cm on general examination was conscious and well-oriented to time, place, and person with average build and gait. On extraoral review, the patient has a symmetrical face with a convex profile and a competent lip. The temporomandibular joints are smooth and well-coordinated, with a regular mouth opening with no rashes or hypopigmented patches. On intraoral examination, the patient was in primary dentition, with bilateral attachment loss in the palatal aspect of the right and left upper second molar (55, 65) and left upper first molar (64) with the presence of local factors (Fig. 1a). There was grade II mobility in the left upper first and second primary molars, whereas grade I mobility was in the right upper first molar. Apart from these, the left lower second primary molar was submerged, and the right-side second molar was clinically missing. There was a weak gingival attachment all over the dentition. An orthopantomogram (OPG) and intraoral periapical radiograph reveal the floating teeth appearance, though the OPG was unclear (Fig. 1b). Further laboratory investigations were carried out, and they showed that there was a decreased hemoglobin content and raised IgG4 levels. Based on the clinical and radiographic findings, a provisional diagnosis of eosinophilic granuloma/LCH over the other differential diagnosis.

Treatment procedure

Under general anesthesia, oral prophylaxis was done, followed by the right upper first and second primary molar extraction and a gingival biopsy; the sample was taken from the buccal and palatal aspects. The crown of the right upper first permanent molar was exposed to the oral cavity; the bone quality was poor and amorphous (Fig. 1c). The tissue sample was sent for histopathological examination, and the final diagnosis of LCH was made (Fig. 1d). The patient was referred to the pediatric hematooncology unit for further management. Further investigations like a skeletal survey, USG abdomen, urine osmolality, and the diagnosis of multifocal oral LCH were made.

The patient was started on slow intravenous vinblastine 3.5 mg for 7 days, Tab Prednisolone 10 mg BD (to be tapered), Syrup Rantec 2.5 mL, and oral hygiene maintenance. During chemotherapy, the patient developed grade I mucositis. After chemotherapy and difficulty swallowing, asymptomatic relief was provided. Currently, the child has completed all cycles of chemotherapy, is asymptomatic, and kept under regular follow-up (Fig. 1e).

Case 2

An 11-month-old male child was reported with a chief complaint of discharge from the ulcer on the lower gum pad and right ear. The patient was normal when the mother noticed multiple white-colored ulcers, mainly on the lower gum pads and right ear. A private practitioner provided symptomatic management. At 5 months of age, a discharge from the right ear with rashes all over the body healed independently and recurred. After pricking the ulcer, there was a discharge, and the child patient was referred to tertiary care. A localized gingival biopsy was taken, followed by computed tomography, a PET CT of the mandible, and a full-body survey (Fig. 2a). The final diagnosis of LCH is a multisystem low-risk disease involving bone, skin, and the right ear. Chemotherapy was started, and the patient's parents were advised to maintain oral hygiene and regular follow-ups. After completion of the first cycle of chemotherapy, within 3 months, the patient again reported the chief complaint of pain and grade III mobility in the left lower second primary molar (75) and right lower first molar (84) and was again referred to our center (Fig. 2a). An OPG was advised and revealed advanced bone resorption, and these teeth were extracted traumatically. After that, a second cycle of chemotherapy was initiated, and the patient remained asymptomatic. However, at 6 years of age, the child was reported to have pain in mobility in the left upper first primary molar (64); an OPG was taken, revealing no recurrence except bone resorption, and the tooth was extracted (Fig. 2b). The patient's parents were informed about the prosthetic replacement of missing teeth, and the child was kept in regular follow-up. The features of two new cases presented in this report are charted in Table 1.

"All procedures performed were by the ethical standards of the institutional and national research committee, with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and after getting written informed parental consent before the treatment."

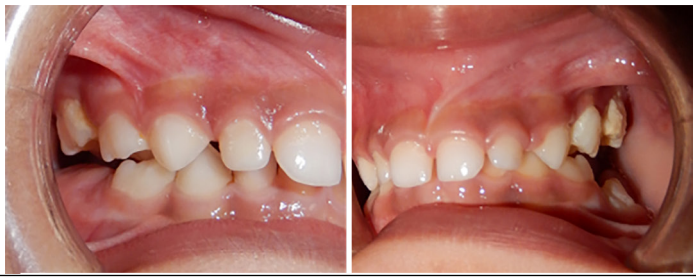
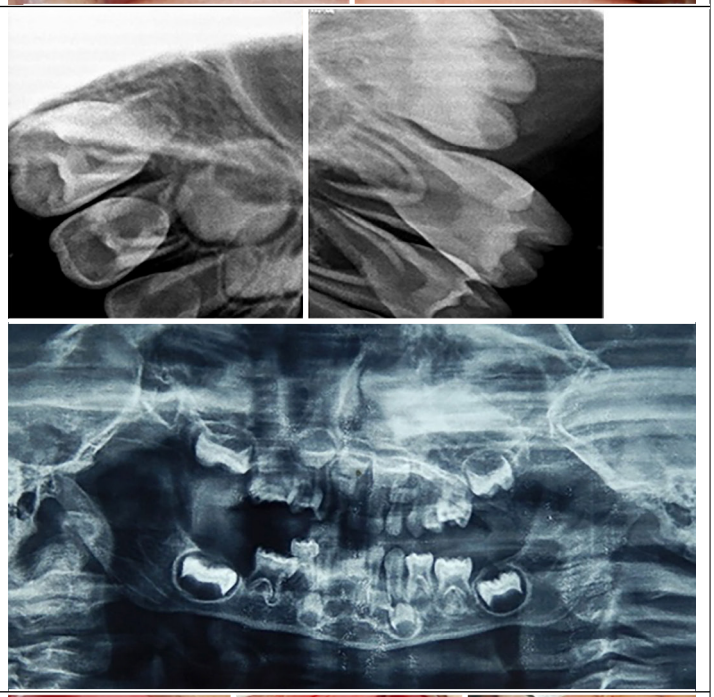
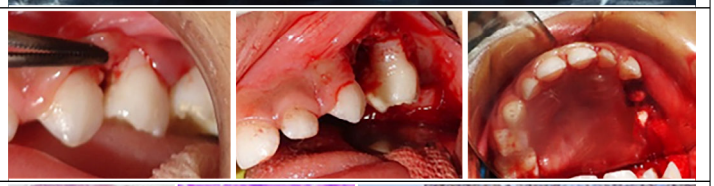
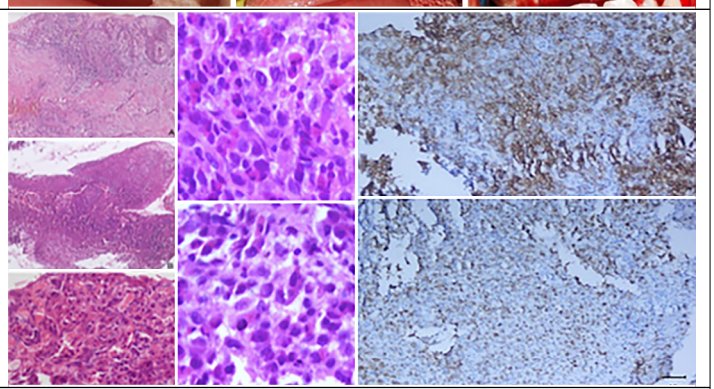
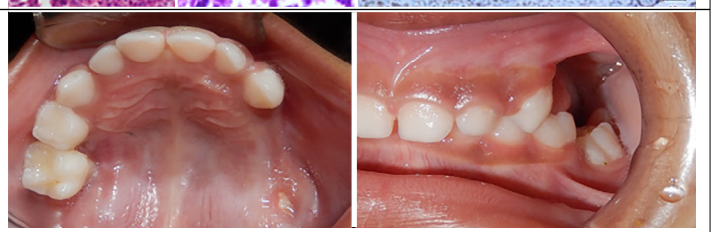
Serial no.	**Case 1**
Figure 1a. Intraoral photographs	
Figure 1b. Orthopantomogram and IOPA of case 1 Full body scan of case 2 after FNAC report findings An orthopantomogram was taken at six when he was referred for examination from pediatrics.	
Intraoperative images	
Figure 1c. Image of biopsy of buccal mucosa of case 1: (a-b) Covering squamous mucosa shows hyperplasia. The sub epithelium shows areas of fibrosis and subepithelial infiltrate [hematoxylin and eosin, ×40] (c) The infiltrate shows tropism from the overlying mucosa [hematoxylin and eosin, ×200] (d-e) Oil immersion image shows histiocytic cells with prominent nuclear grooving and folding. A dense eosinophilic infiltrate is mixed with these cells. [hematoxylin and eosin, ×1000] (f) Immunochemistry staining CD1and langerin.	
Figure 1d. Follow-up images after seven cycles of chemotherapy of case 1	

Table 1. The features of two new cases presented in this report are charted for ease of comprehension

		Case 1 (Figure 1)	**Case 2 (Figure 2)**
Presentation	Age/sex	2.5 Year/Fch	11 month/ Mch
	We were first reported (to the Outpatient Unit of pediatric dentistry at our Institute	March 2016	June 2011
	Chief Complaint	Pain and bleeding from the upper left back teeth	Pain and pus discharge from rupture of a single whitish ulcer on the right lower gum pad and multiple small ulcers on the hard palate
History of presenting illness	Symptoms	Pain while eating and brushing, food lodgment; 6–7 months ago	The mother first noticed Pain and ulceration when the child was 2 months of age.
	Action taken	• Gingival massage ointment prescribed by a private practitioner	• Same
		• No relief- 1 month later, referred to our tertiary center	
Medical history		• Rashes in the scalp at around 1½ years of age	At the age of 5 months • Discharge from the right ear • Recurrent rashes all over the body that healed on their own
		• Red rashes on stomach and back typically described as "grains of pomegranate" since 1½ months of presentation	
		• Inflammation of the external genitalia	
		• Hospitalized for 1 day with pneumonia at the age of 6 months	
Examination	General	No outstanding findings	
	Extraoral		
	Intraoral	• Bilateral gingival attachment loss	
		• Plaque + Calculus+	
		• 55 - Grade I mobility	
		• 64, 65 - Grade II mobility	
		• 75 - submerged	
		• 85 - clinically missing	
		• Weak gingival attachment all over the dentition	
Investigations (ordered by unit of pedodontics)	Radiographic evaluation	OPG • Floating teeth appearance	Nil
		CT scan	• An expansile lesion 1.61cms in size involving the body of the right mandible and causing bony expansion of the mandible with cortical destruction along the lingual and buccal surfaces
			• The lateral and anterior cortices also showed scalloping and cortical thinning with an outward displacement of associated teeth
		PET-CT	• Mild focal FDG avidity is seen in the following region
			• Soft tissue fullness in the left maxillary sinus with the erosion of the medial wall and floor of the left orbit.

Table 1. Cont.

		Case 1 (Figure 1)	Case 2 (Figure 2)
Investigations (ordered by unit of pedodontics)	Radiographic evaluation	PET-CT	• Lateral wall and inferior wall of the right maxillary sinus with soft tissue component and first molar teeth bilaterally
			• Sign of metabolically active disease
	Laboratory investigations	Low Hemoglobin and IgG4	Nil
		FNAC	FNA smears from the hard palate mass are cellular and show numerous scattered histiocytes, with a large nucleus with nuclear grooving and abundant basophilic cytoplasm in the background.
	Provisional diagnosis	LCH	LCH
	Biopsy site	Gingivae of buccal and palatal aspect of 64 65	Three intraoral sites of the hard palate
	Remarks	• Procedure is done under general anesthesia, keeping in mind the pre-cooperative age of the child	
		• Extraction of 64 65	
		• Oral prophylaxis	
		• Bone quality is amorphous and poor	
		• Crown of 26 was exposed to the oral cavity	
	Histopathology	Numerous histiocytes with intranuclear grooving surrounded by a cluster of eosinophils	Dense inflammatory infiltrates eosinophils, atypical histiocytes, few polymorphs, and a lining of stratified squamous epithelium predominately.
	Immunohistochemistry	S100 positive	S100 positive CD3 negative
Final diagnosis		Multisystem LCH	Multisystem LCH (low-risk disease involving bone, skin, and right ear)
Referral		Pediatric hemato-oncology	
Further investigations		Skeletal survey - N USG abdomen - N Urine osmolality - N	PET - involvement of maxillary sinuses, orbit bilaterally, and sphenoid bone FNAC - LCH
Management		Chemotherapy regimen: iv vinblastine 3.5 mg tab Prednisolone 10 mg	
Complication		Grade I mucositis in the oropharynx, difficulty in swallowing-palliative management	Nil
Relapse		Nil	• Within 3 months, the patient presented with pain and grade III mobility of 75, 84
			• OPG- advanced bone loss around 75, 84 seen, atraumatic extraction carried out
			• At 6 years of age, pain and mobility with 64
			• OPG- bone resorption and extraction carried out
Follow-up		5 years- Remission, under follow-up	10 years- Remission, under follow up

OPG: Orthopantomogram; PET-CT: Positron Emission Tomography–Computed Tomography; FNAC: Fine Needle Aspiration Cytology; LCH: Langerhans cell Histiocytosis

Serial no.

Case 2

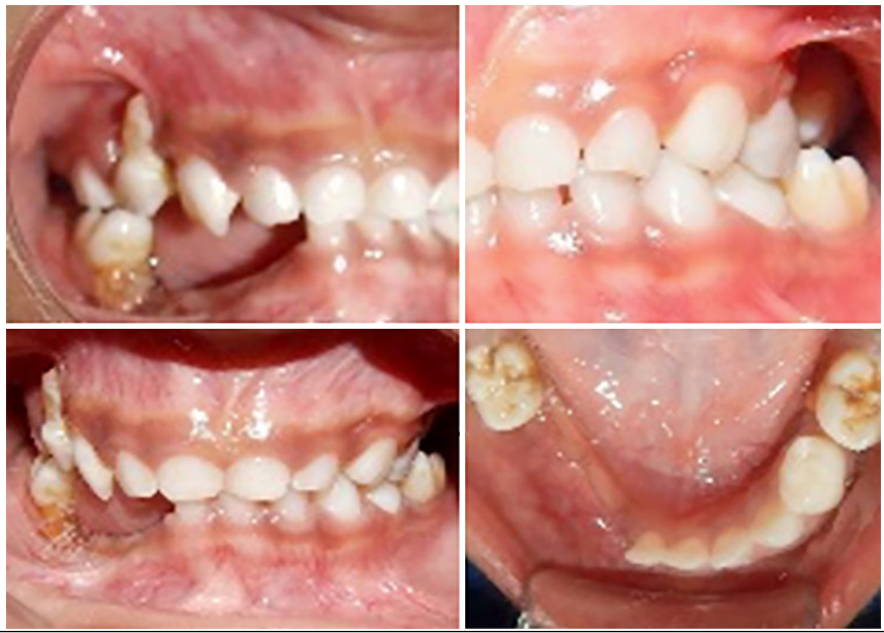


Figure 2a. Intraoral photographs

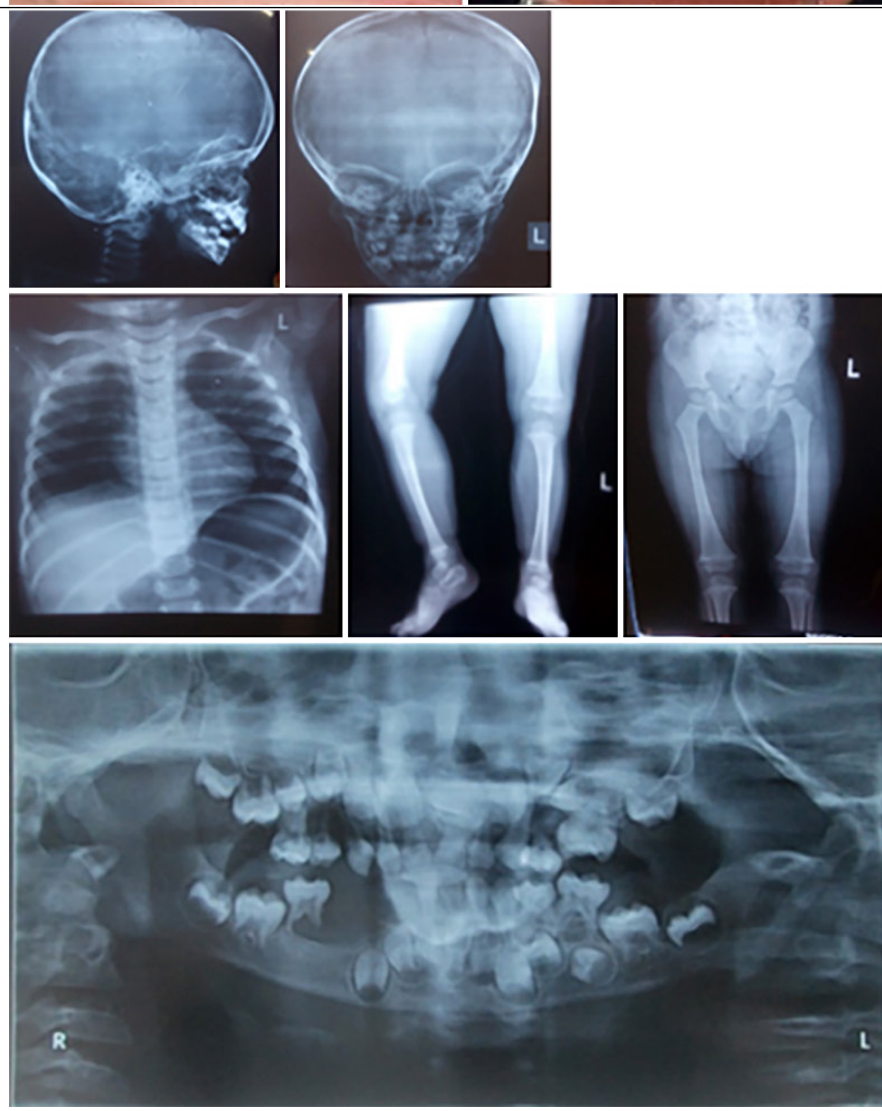


Figure 2b. Orthopantomogram and IOPA Full body scan of case 2 after FNAC report findings.
An orthopantomogram was taken at 6 years of age when he was referred for examination from pediatrics.

Table 2. Differential diagnoses of pediatric oral Langerhans cell histiocytosis

	Differential diagnosis	Feature of alternate diagnosis	Feature of LCH
Oral mucosal lesions	Trauma	History of traumatic injury	No such history
	Papillon-Lefevre syndrome	Hyperkeratosis of palms and soles	Seborrheic skin lesions or atopic dermatitis
	Hypophosphatasia	Low serum alkaline phosphatase levels and excessive excretion of phosphoethanolamine in the urine Large pulp spaces, and premature loss of teeth start from the anterior mandibular region.	Posterior teeth are invariably affected. When anterior teeth are affected, it is generally an extension of posterior lesions.
	Aggressive Periodontitis	*Actinobacillus actinomycetemcomitans* in subgingival culture	Scooped out lesions with some crestal bone intact May have sclerosis or bone neoformation in the osteolytic lesions
	Leukemias, Lymphomas, Cyclic Neutropenia, Agranulocytosis	Distinction based on altered laboratory findings	
	Tuberculosis, Sarcoidosis and other giant cell disorders	Tissue biopsy positive for S100, CD1a and CD207 in LCH	
Bone lesions-Unifocal	Odontogenic cyst	Dentigerous cysts may be associated with developing tooth germs Aspiration will yield fluid	Tissue biopsy positive for S100, CD1a and CD207 Aspiration will not yield fluid
	Periapical lesions	Associated with carious tooth	Usually intra-bony, not involving the alveolar bone, associated teeth if any may or may not be sound
	Fibrous dysplasia	Cherub looks or eyes-raised-to-heaven look with facial swelling Painless	Swelling without cherub look May be painful or Painless
	Giant Cell Granuloma	Lesion crosses midline	Mainly seen in body and ramus of mandible
Bone lesions-Multifocal	Osteomyelitis	Cultures from biopsy sample: positive for bacteria or atypical mycobacteria	Tissue biopsy positive for S100, CD1a and CD207
	Ewing's Sarcoma	Radiographically, strong periosteal reaction with onion skinning seen	Bone neoformation, sclerotic rim in case of healing lesions
	Hyperparathyroidism-brown tumor	Distinction based on altered laboratory findings	
	Multiple keratocystic odontogenic tumor	Scalloped margins of osteolytic lesions	Well defined non corticated, poorly-defined or invasive margins.

LCH: Langerhans cell Histiocytosis

Discussion

This case series aims to elucidate the difficulties encountered with this uncommon disease and create a roadmap for management.

LCH is a rare disease with a peak incidence of 0.5–5.4 cases per million people per year. It is predominantly a disease of childhood, with more than 50% of patients diagnosed between the ages of one and 15 years.[2,3] There is a peak in the incidence between the ages of one and four.[4] The clinical presentation can differ from single or multifocal bone lesions to disseminated bone disease with multiorgan involvement. The disease most frequently manifests as osseous lesions, characteristically involving the flat bones of the skull, ribs, pelvis, and scapula. In the oral cavity, LCH can present as bone, mucosal, and periodontal lesions. In addition, the literature on manifestations in the oral region is limited and mainly consists of case reports or retrospective series. According to the Histiocyte Society, patients with oral and craniofacial bone involvement are more likely to develop diabetes insipidus during their course. They are classified as CNS-risk lesions.[5] Hence, oral lesions must be accurately diagnosed because more significant implications exist if they are missed. The differential diagnosis of LCH includes a plethora of conditions. Table 2 describes the features necessary to arrive at a definitive diagnosis. The clinical prognosis of patients worsens with the growing

Table 3. Previously reported cases of LCH in the literature

Study ID	Description	Comments
Can et al (2005)[2]	Lytic lesion in jaw, when referred and consulted with dentist it was regarded as having no relation with dental disease	Possible lack of awareness
Shooriabi et al (2016)[6]	"Mouth ulcers" treated for 6 months with oral ketoconazole, benzydamine and chlorhexidine mouthwash, nystatin suspension prescribed by different physicians with no remission. Diagnosis was finally established by biopsy.	Sooner Biopsy - more good than harm.
Neckel et al (2019)[8]	6-month-old Fch was diagnosed by biopsy under general anesthesia was treated unsuccessfully for 2 months prior to diagnosis as thrush and osteomyelitis or aseptic necrosis. Three primary teeth were extracted in this context. The disease was refractory to conventional treatment.	Timely referral and earlier biopsy could have led to earlier diagnosis In view of the refractory nature of the disease, earlier institution of systemic therapy would have benefitted the patient
Ramos-Gutiérrez et al, (2016)[9]	2 years, 8 months girl presented to the "strongly decayed, painful teeth and gum bleeding". She had recurrent episodes of skin erythema and rash, otitis media, anemia and fever.	Vigilant to discern dental and mucosal abnormalities in their patients with suspected LCH.
Whitsett et al (1999)[10]	"Dental problems" and jaw tenderness on original presentation, followed by diagnosis by h/o central diabetes insipidus after 1 year	Dental evaluation could have led to earlier diagnosis
Alajbeg et al (2006)[11]	2.5-year-old Mch, substantial erythema and ulcerations on palatal, buccal, and alveolar regions. It took two subsequent visits in 6 months intervals and re-evaluation at pediatric oncology clinic where diagnosis was finally established	Diagnosis at early stage by dentist could have prevented involvement of other organ systems. Biopsy- better than harm
Murray et al (2011)[12]	Swelling on upper gums for 7 months. Mother had taken him to see the same general dentist 6 times over the 7-month period. Did not obtain any biopsy specimens	Lack of awareness. Biopsy - better than harm.

Fch: Female child; Mch: Male child; LCH: Langerhans cell Histiocytosis

number of involved organs, with an increasing number of organ dysfunctions, rapid disease progression, limited treatment response, and a decreasing age of first disease manifestation.[2] Concerning oral presentations, involvement of anterior teeth also indicates a worse prognosis. LCH may be self-limiting or locally recurrent, but high-risk systemic cases may have fatal outcomes. Recurrence rates are reported to range from 1.6% to 25%.[2]

Both of the current cases present abnormal mobility of deciduous teeth. As in the first case, an additional history of rashes on the scalp and trunk, which general practitioners frequently dismiss as being common in children when presenting with concomitant oral manifestations, must alert the pediatric dentist to a diagnosis of LCH since they may often be the first to examine a child's oral cavity, especially since LCH may be fatal in severe cases.

Appropriate referral by general practitioners, pediatricians, and other specialists who encounter oral lesions to pediatric dentists for diagnosis and, in turn, after diagnosis, by pediatric dentists to pediatric hemato-oncologists and maxillofacial surgeons, if indicated, for a subsequent multidisciplinary treatment approach with regular follow-up, are imperative in the management of such exceptional cases.

The uncommonness of the disease, varied presentation, vast possibilities of differential diagnoses, profound prognostic implications, frequent recurrence, and the need for interdisciplinary coordination create a situation like the elephant and five blind men, thus posing a unique challenge in the overall management of such cases.

Over the decades, authors have acknowledged missed dental diagnoses in pediatric oral LCH and highlighted the importance of early diagnosis. The diagnosis of LCH is based on the histological and immunophenotypic examination of lesional tissue.[5,6] According to the Histiocyte Society, only in the case of isolated vertebra plana lesions without a soft tissue component does the risk of biopsy outweigh the need for a tissue diagnosis.[7] Keeping in mind the significant implications of the disease, we suggest that, when in doubt, an incisional

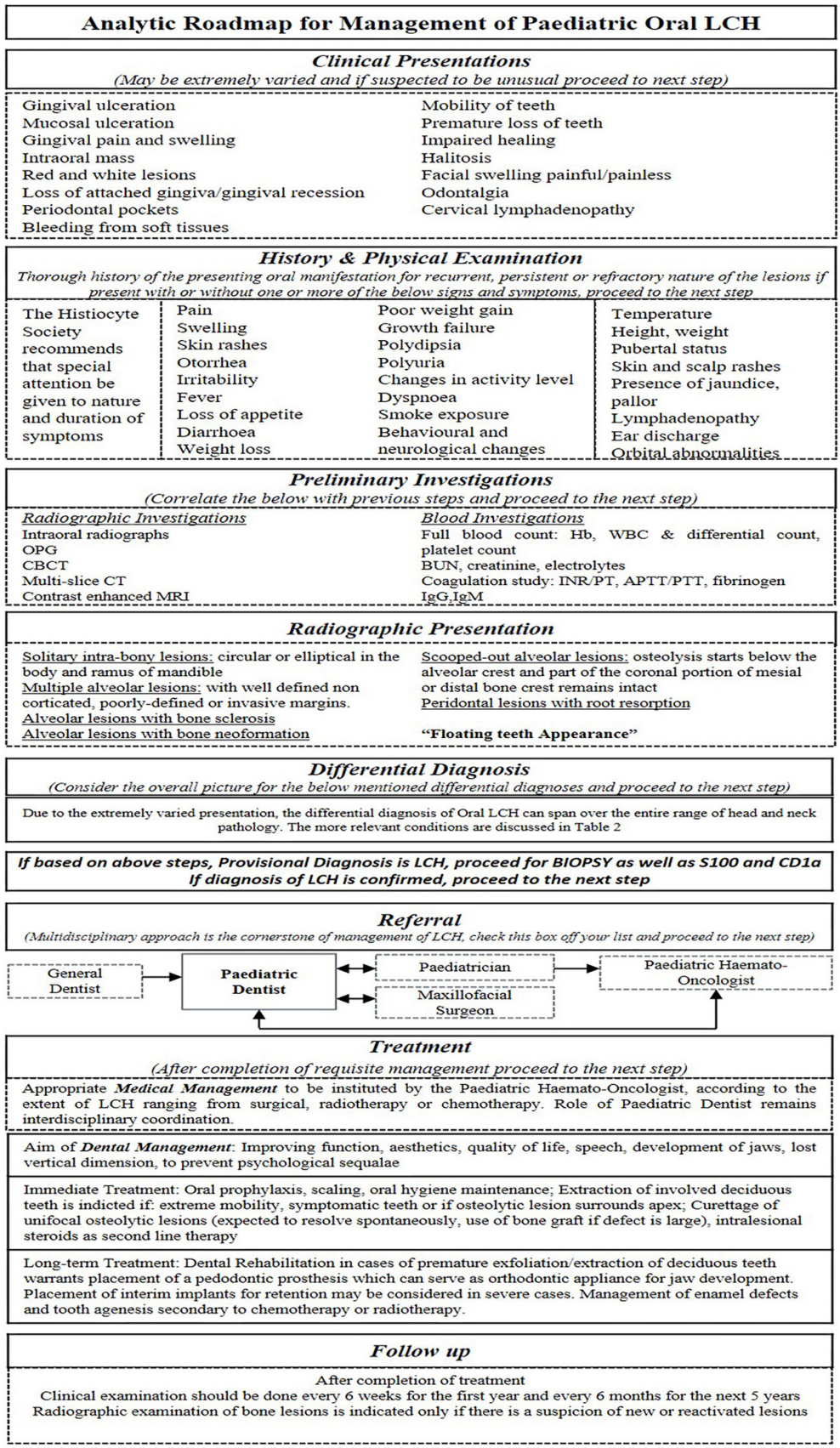


Figure 3. Analytic roadmap for management of pediatric oral Langerhans cell Histiocytosis (Created by authors)

biopsy be taken for suspicious oral lesions in preference to a wait-and-watch approach since systemic oncologic management, if instituted early in the course of the disease, will offer much more benefit compared to the negligible risk imposed by an incisional biopsy. In support of this suggestion, cases previously reported in the literature are discussed in Table 3, where the approach of early biopsy could have improved the total outcome.

In pertinence to this issue, we have endeavored to formulate a roadmap to avoid missed diagnosis situations by oral health care professionals. It provides a step-by-step approach exhaustively covering aspects that fall under the jurisdiction of pediatric dentists to assist in the diagnostic hurdles faced due to the challenging presentation of this condition. This would help pediatric dentists, other oral health care professionals, and physicians across other specialties (Fig. 3).

The roadmap provided in this article attempts to assist pediatric dentists and other healthcare professionals in the early diagnosis of pediatric oral LCH. However, since this is a scarce condition, there is an urgent need to collate multi-centric and multi-country data to enable the experts to formulate clinically useful guidelines regarding stratifying the diagnostic approach in terms of conservative versus aggressive means to allow the oral health care professionals to take appropriate rapid steps for catching the disease early.

Why this paper is essential for the pediatric dentist

- Early oral manifestations of LCH present a unique prospect for pediatric dentists to contribute to its diagnosis
- A roadmap designed to aid in diagnosing oral LCH is presented
- With the oral cavity being the mirror of general well-being and being the first point of contact, pediatric dentists must have sound knowledge, carefully examine oral lesions, and take prompt action, thus becoming pivotal in diagnosing various systemic conditions
- Pediatric dentists play an important role in educating the parents about the disease, the treatment, and the possible outcome and referring the patients to specialty centers for appropriate treatment.

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Conflict of Interest: None declared.

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