Case Report

Langerhans Cell Histiocytosis – A Challenge for the Dental Professional

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Abstract

Langerhans cell histiocytosis (LCH) is a group of rare disorders histologically characterized by the proliferation of LC, involving multiple organs and systems. Typically, there is bone involvement and, less frequently, lesions may be found in the lungs, liver, lymph nodes, skin, and mucosae. Oral soft tissue lesions without bone involvement are rare. Antigenic markers that react with CD1a glycoprotein, cytoplasmatic protein S100 detected by immunoperoxidase staining, and/or presence of Birbeck granules on electron microscopic examination are required for a definitive diagnosis of LCH. In this article, we report a case of LCH, which had presented with multiple oral lesions without any other systemic signs and symptoms. Management of such children with periodontal manifestations should include hematological and, if possible, immunological investigations at an early stage. Careful clinical examination, good diagnostic skill, and awareness of characteristic cytological features of LCH can lead to earlier diagnosis and treatment with minimal deformity.

Keywords: Histiocytosis-X, Langerhans cell, oral manifestations, periodontitis

Introduction

Langerhans cell histiocytosis (LCH) has replaced the older term histiocytosis X that encompassed three entities: eosinophilic granuloma, Hand–Schuller–Christian disease, and Letterer–Siwe disease.[1] The Letterer–Siwe syndrome is an acute disseminated form, characterized by cutaneous lesions, hepatomegalies, splenomegalies, and ganglionic hypertrophies, usually occurring in infants and newborns. Bone lesions occur in the skull, long bones, and mandible. Lesions in the mandible show definite radiolucent image that may mimic both juvenile and severe periodontal disease.[2]

The Hand–Schuller–Christian syndrome is a chronic disseminated form characterized by a triad of symptoms: exophthalmos, diabetes insipidus, and osteolytic lesions in the skull. Increased gingival volume and bleeding, deep pockets, alveolar bone loss, and tooth mobility resembling periodontitis, characterize oral involvement. Earliest signs of this disease usually manifest during childhood.[2] Solitary bony lesions of ribs, pelvis, or mandible characterize eosinophilic granuloma.[3]

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Case Report

A 15-year-old male patient reported to the Department of Periodontics, JCD Dental College, Sirsa, Haryana, complaining of intense pain, burning sensation and difficulty in chewing, swelling of gums, and bleeding from gums since 4 months. Dental and medical history of patient's family was nonsignificant. His medical history was unremarkable except for a vague abdominal pain, for which a physician's expert advice was sought and abdominal ultrasonography was noncontributory.

Clinical Examination

Intraoral examination revealed poor oral hygiene, with halitosis and hyperplastic gingiva. Gingiva was erythematous, fiery red in color, and gingival volume was increased. Gingival enlargement was sessile, diffuse, and fragile with punched out interdental papilla in relation to lower anterior teeth (31,41)

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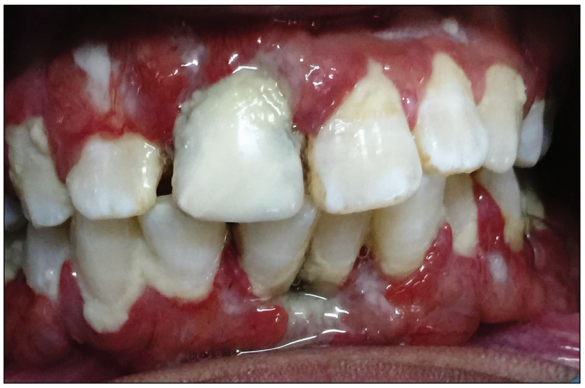


Figure 1: Poor oral hygiene and missing interdental papilla in relation to lower anteriors

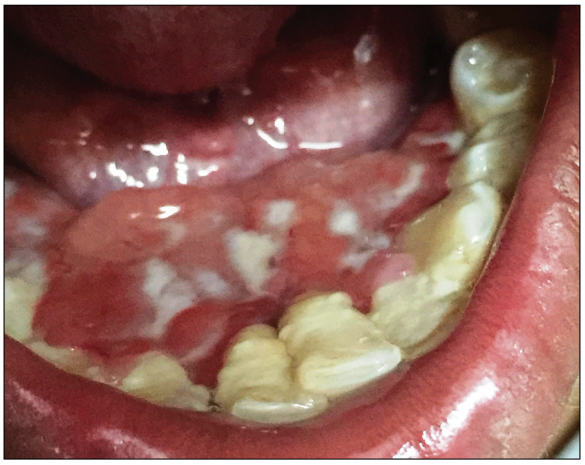


Figure 2: Necrotic ulcerations with pseudomembranous slough

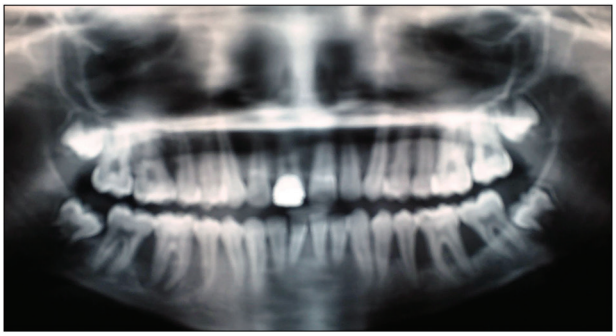


Figure 3: Orthopantomography

[Figure 1], with generalized palatal/lingual, buccal multiple necrotic ulcerations covered with pseudomembranous slough [Figure 2], and coated tongue. Spontaneous and profuse bleeding from gingiva was noted.

On periodontal examination, generalized deep periodontal pockets (4–12 mm) in all sextants were seen. Generalized severe tooth mobility varying from grade I to grade III was recorded. Orthopantomography revealed generalized alveolar bone loss [Figure 3].

Further hematological and biochemical investigations revealed normal results except for raised alkaline phosphatase [Tables 1 and 2]. Patient had a normal blood profile and his liver function test, coagulation profile, thyroid profile, and urine analysis were normal. PA view of the skull and general skeletal radiograph survey showed no other lytic lesion in the body. At this time provisional diagnosis of acute necrotizing ulcerative gingivitis or pubertal periodontitis was made.

Treatment comprised of intensive oral hygiene instructions with full mouth oral prophylaxis and use of hydrogen peroxide mouthwash with 1:3 dilutions. Tab Doxycycline 100 mg was administered for 2 weeks with two tablets on first day followed by one tablet daily. Initial clinical improvement was seen, but 1 week later, further deterioration occurred.

Table 1: Complete blood investigations report

S. No	Test name	Result	Normal value
1	Total bilirubin	0.64	0.2–1.2 mg/dL
2	Direct bilirubin	0.28	Upto 0.25 mg/dL
3	Indirect bilirubin	0.36	0.2–0.8 mg/dL
4	SGOT	18.6	5–34 IU/L
5	SGPT	24.2	0–31 IU/L
6	**Serum alkaline phosphatase**	**706.7**	**106–308 IU/L**
7	Total protein	6.18	6.6–8.8 g%
8	Albumin	3.03	3.5–5.2 g%
9	Serum Globulin	3.15	2.3–3.5 g%
10	Hemoglobin	11.7	13.0–17.0 g/dL
11	TLC	10400	4000–11000/mm^3
12	Neutrophils	70	40–75%
13	Lymphocytes	25	20–50%
14	Eosinophils	3	1–6%
15	Basophils	0	0–1%
16	Monocytes	2	2–10%
17	Platelet count	5,12,000	1.5–4.0 lakhs/mm^3
18	Total RBC count	4.9	4.5–6.5 million/mm^3
19	PCV	36	43–54%
20	MCV	72	76–96 mm^3
21	MCH	23	27–32 pg
22	MCHC	32	30–25%
23	ESR	36	0–15 mm at 1 h
24	Hepatitis B	Negative	
25	Serum iron	78.25	65–175 µg/dL

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, TLC: Total leukocyte count, RBC: Red blood cell, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, ESR: Erythrocyte sedimentation rate

Table 2: Thyroid profile test

1.	T3	1.13	0.82–2.13 ng/mL
2.	T4	9.50	5.60–11.70 µg/dL
3.	TSH	2.54	0.70–6.40 µIU/mL
4.	Intact parathyroid hormone	18.62	9–69 pg/mL

T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone

Table 3: Real-time quantitative PCR for detecting *Mycobacterium tuberculosis* complex and ANA Western blot profile (by ELISA)

1. *Mycobacterium tuberculosis* (real-time PCR)	**Not detected**
ANA Western blot profile (by ELISA)	
1. SS – A	19 IU/ml less than 30 IU/mL
2. Anti Ro. Ab	24 IU/ml less than 40 IU/mL

PCR: Polymerase chain reaction, ELISA: Enzyme linked immunosorbent assay, ANA: Anti nuclear antibodies, SS – A: Anti-Sjögren's-syndrome-related antigen A, Anti Ro. Ab: Anti-nuclear autoantibodies associated with systemic lupus erythematosus

Table 4: Immunofluorescence assay

	Autoimmune immunofluorescence assay		
1	Antinuclear antibodies	0.50	<1.50 Index value negative >1.50 Index value positive
2	Antineutrophil cytoplasmic AB (ANCA)		
	P-ANCA	Negative	Negative
	C-ANCA	Negative	Negative
3	Antiphospholipid antibody (IgM)	5.27	<15 U/mL negative >15 U/mL positive

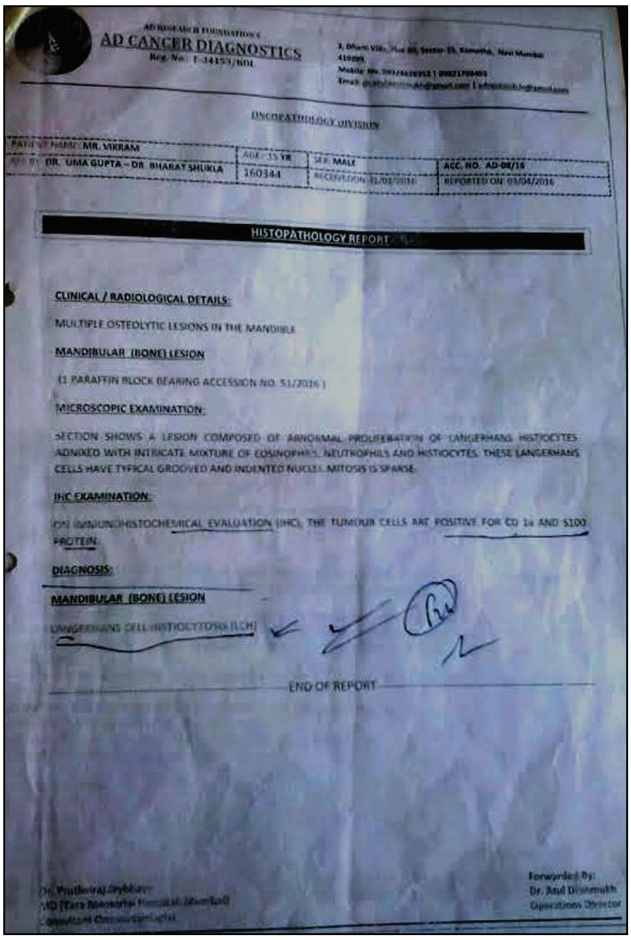
AB: antibodies, ANCA: Antineutrophil cytoplasmic antibodies, P-ANCA: Perinuclear anti-neutrophil cytoplasmic antibodies, C-ANCA: Cytoplasmic anti-neutrophil cytoplasmic antibodies, IgM: Immunoglobulin M

Despite intensive oral hygiene measures and reinforced brushing habits, inflammation failed to resolve. Excisional biopsy of the gingival lesion, therefore, was undertaken which was then sent for histopathological examination and further investigations such as real-time quantitative polymerase chain reaction (PCR) for detecting *Mycobacterium tuberculosis* complex and ANA Western blot profile (by ELISA) were done to rule out systemic conditions involving periodontium such as tubercular gingivitis and HIV. *Mycobacterium tuberculosis*-PCR was negative and HIV antibody test was nonreactive. Immunofluorescence assay was done to rule out autoimmune diseases [Tables 3 and 4].

Histopathological examination revealed a lesion composed of abnormal proliferation of Langerhans histiocytes admixed with intricate mixture of eosinophils, neutrophils, and histiocytes. These LC have typical grooved and indented nuclei. Mitosis is sparse. On immunohistochemistry, large cells showed positivity for S-100, CD1a proteins [Figures 4 and 5]. Based on clinical, histological, and immunohistochemical features, LCH was diagnosed and confirmed.

Discussion

Alveolar bone loss in young children is clearly a serious finding. Gingival lesions could be one of the first manifestations of LCH. Clinically, it is difficult to distinguish oral LCH lesions from bone metastases,


AD CANCER DIAGNOSTICS

HISTOPATHOLOGY REPORT

CLINICAL / RADIOLOGICAL DETAILS:

MULTIPLE OSTEOLYTIC LESIONS IN THE MANDIBLE

MANDIBULAR (BONE) LESION

MICROSCOPIC EXAMINATION:

IHC EXAMINATION:

DIAGNOSIS:

MANDIBULAR (BONE) LESION

END OF REPORT

Figure 4: Histopathology report

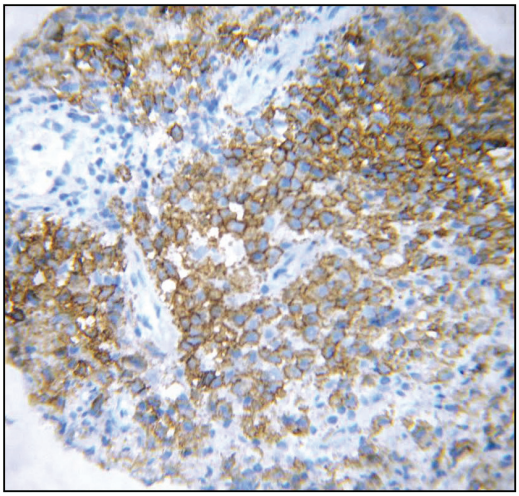


Figure 5: Langerhans Cell Histiocytosis - Immunostatin

lymphoma, ulceration by HIV infection, vasculitis, and simple chronic periodontal inflammation.[4]

This case report illustrates a problem of diagnosis and management particularly relevant in children. Prepubertal periodontitis is not common, but may occur in conjunction with systemic states such as juvenile onset diabetes, hyperparathyroidism, adrenocortical hyperfunction,

scleroderma, Histiocytosis "X," Papillon–Lefevre syndrome, leukemia, and neutropenia.[5]

In this case, nothing from the initial clinical, radiological, or hematological investigations suggested any of the above-mentioned diseases. In particular, the pattern of bone loss resembled that seen in adolescents with juvenile periodontitis. Another feature suggestive of the diagnosis of prepubertal periodontitis unrelated to any specific systemic condition was the initially reasonably favorable response to scaling together with the administration of doxycycline. Failure of these measures to eliminate inflammation completely at a later stage favors the diagnosis of periodontitis as a manifestation of systemic disease.

Several authors have noted that oral lesions are common early findings in histiocytosis, and it is also known that oral symptoms may predate other evidence of the disease by as much as 10 years. Therefore, in children who present with features of prepubertal periodontitis, the differential diagnosis should always include Histiocytosis "X."[5]

Etiology of LCH is unknown but theories suggest a role for environmental, infectious, immunologic, genetic causes, and a neoplastic process.[6] Main feature of LCH is abnormal proliferation of the antigen-presenting LC. Immunological abnormalities resulting from suppressor cell deficiency have been suggested as a cause, explaining the LCH a result of production of pathologic phenotype of langerhans cells and their actions. New data suggest that abnormal immunological response may be the result of viral infection of lymphocytes, with special reference to HHV-6.[7]

Pathophysiology of LCH involves histiocytes, cells derived from monocytes of granulocyte/macrophage series after extravascular diapedesis.[3] Pathologic LC are characterized by the presence of antigenic surface markers that react with specific monoclonal antibody and by histologic presence of Langerhans granules called Birbeck's granules (rod-shaped ultrastructural organelles having vesicular portion giving it a "tennis racquet" appearance under electron microscopy).[3]

For this patient, definitive diagnosis was based on immunohistochemical analysis. S-100 and CD1a positivity are hallmarks of LCH, which were evident in our case.[8] In this case, oral lesions were treated by topical corticosteroids – clobetasol propionate – 0.05%, as used by Manfredi *et al.*,[9] and topical antifungal (miconazole oral gel) was used to avoid oral candida infections. Patient underwent frequent professional oral hygiene sessions to minimize mucosal and periodontal damage, and meanwhile patient was referred to an oncologist, where he was advised chemotherapy (methotrexate and vinblastine with prednisone).

Clinical Significance

Sound knowledge of LCH can change the clinician's traditional method of handling periodontal manifestations in pediatric patients.

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