

CASE REPORT

Multisystem Langerhans cell histiocytosis presenting as an oral lesion

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare proliferative disorder in which the pathologic Langerhans cells infiltrate and destroy the tissues. Patients with LCH present varied clinical manifestations. Cutaneous lesions in LCH manifest as vesiculopapular eruptions that often mimic various infectious diseases particularly in infants. We present a case of a female infant with an ulcerative lesion intraorally. The baby was asymptomatic otherwise. A detailed history revealed the presence of cutaneous lesions that was overlooked by her parents. **Conclusion:** This report tries to briefly discuss the current concepts regarding the etiology of LCH. An attempt has been made to emphasize the need for a thorough systemic examination. The protocol of investigative procedures to be adopted in LCH is also discussed.

Key words: CD1a, Langerhans cell histiocytosis, oral cavity, S100, ulcerative lesion

INTRODUCTION

Multisystem Langerhans cell histiocytosis (LCH) may present only as an oral lesion. This report tries to outline the significant role of a dental practitioner in recognizing the varied manifestations of this rare disorder.

The histiocytoses are a group of disorders characterized by the proliferation of cells of the mononuclear phagocyte system (MPS).^[1] Langerhans cells (LC), which are a part of the MPS are dendritic cells that can process and present antigens to the T-cells. These cells are found in the skin, mucosal lining of the oral, ocular and vaginal surfaces, lymph nodes and spleen.^[2] LC originate from the bone marrow derived monocyte precursors.^[3]

LCH is a rare proliferative disorder of unknown etiology in which there is an accumulation of pathologic LC.^[4] LCH was originally termed as histiocytosis-X by Lichtenstein in 1953. The etiology of the lesion is still elusive, and the question of whether LCH is a reactive or neoplastic disorder remains unanswered.^[3]

In this paper, we report a rare case of an 8-month-old female patient who presented to a general dental practitioner with a complaint of only an ulcerative growth in the oral cavity. Eventually the course of the disease was very aggressive, and in spite of initiating treatment the death of the patient was inevitable. It is our purpose to emphasize the critical role of dentist in recognizing this rare disorder, which can present primarily as an oral lesion and the necessity of subjecting such cases for a thorough systemic evaluation and early treatment. We also tend to discuss the current concepts in biology and advances in the treatment modalities.

CASE REPORT

Clinical features

An 8-month-old female patient was brought to the dentist by her mother with a complaint of an ulcerative growth in the hard palate. Her mother had noticed an erupting tooth in the anterior part of the upper gums when the patient was 3 months old. She also noted a small ulcerated swelling in the same region about 3 months ago. The lesional area was impacted with food debris resulting in foul odor. There was bleeding from the lesional site on manipulation. There was no other complaint except for occasional mild rashes on the scalp and trunk. The patient was afebrile, and active with no disturbance during sleep.

On examination, there were no significant extra-oral findings. Intra-oral examination revealed an ulcerative growth present

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in the alveolus of the right maxilla extending from the region of 51 to 55 t and also extending onto hard palate, measuring 1.5 cm × 1.5 cm in size. The ulceration had a raised edge. The crown of 52 was noted within the lesion and was mobile [Figure 1]. The other teeth present in the oral cavity were the erupting 71 and 81. The clinical impression was a slow growing ulcerative lesion of the right maxillary alveolus extending onto the hard palate.

Radiological features

The posterior-anterior and lateral skull views showed a cystic lesion present in the right maxillary region, and a radiological diagnosis of a maxillary alveolar cyst was given. There was no lesion extending to the skull vault.

Computed tomography (CT) scan showed a nearly spherical mass in the right side of the palate measuring 1.37 cm (anteroposteriorly) × 1.44 cm (width) × 0.63 cm (height). Destruction of the adjacent alveolar process of the maxilla and anterior aspect of the hard palate on the right side was noted along with the loss of normal bony crypts of upper teeth. Tooth 52 was pushed out prematurely. Multiple enlarged lymph nodes were observed in the neck bilaterally. No focal lesion was seen in the visualized lung apices.

Pathological features

Blood investigation showed no significant findings. During biopsy, all the crowns of the developing teeth were seen floating within the lesion. The dental surgeon was unable to separate the lesion from the surrounding normal tissue; hence tissue had to be obtained as piecemeal.

The gross specimen consisted of one large and several small soft tissues. All the soft-tissue bits were white to dark brown in color and firm in consistency. The largest tissue measured 1.3 cm × 0.3 cm × 0.6 cm while, the smaller soft-tissues collectively measured 1.0 cm × 0.3 cm × 0.6 cm in size.

Microscopically the soft-tissues showed ulcerated hyperplastic parakeratinized stratified squamous epithelium with a moderately collagenous connective tissue stroma that was diffusely infiltrated with pale staining cells resembling histiocytes. The lesional cells had an indistinct eosinophilic cytoplasm and exhibited indentation of nuclei. Varying numbers of eosinophils, lymphocytes and plasma cells were interspersed among the lesional cells [Figure 2]. Abundant hemorrhagic foci were evident. The lesional cells stained positive for S100 and CD1a [Figure 3]. Odontogenic epithelial cells, dentine and enamel matrix were also present. As the lesional cells were positive for CD1a a diagnosis of LCH was confirmed.

Our patient was referred to the oncology department where she was staged as a multisystem high risk case. Our patient



Figure 1: An ulcerative growth present in the alveolus of the right maxilla with the crown of 52 noted within the lesion

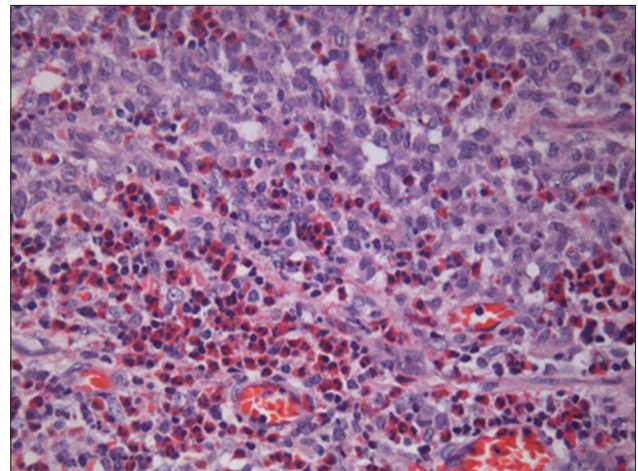


Figure 2: Lesional cells with indistinct eosinophilic cytoplasm and exhibiting indentation of nuclei admixed with eosinophils, plasma cells and hemorrhagic foci (H and E, original magnification ×400)

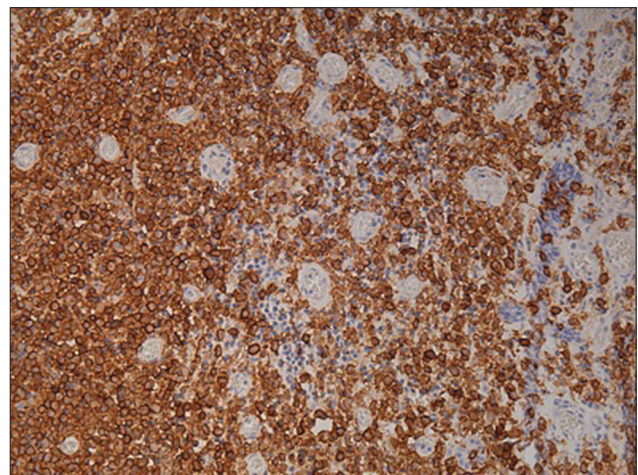


Figure 3: Lesional cells stained positive for CD1a (Immunoperoxidase envision technique, original magnification ×400)

was totally asymptomatic with the multisystem involvement being totally unrecognized leading to delay in parents seeking

treatment. The patient was placed under ARM B protocol for LCH consisting of an initial treatment with prednisolone, vinblastine, etoposide and a continuation treatment with oral 6-mercaptopurine followed by pulses of oral prednisolone, vinblastine and etoposide. Despite the treatment plan adopted, the baby succumbed to her disease within 6 months after the initial diagnosis.

DISCUSSION

The histiocytoses encompass a wide range of conditions that may be primary or secondary, solitary or multiple, benign or malignant and may be classified into LCH, non-LCH and malignant histiocytic disorders.^[5] LCH is a rare disease in which the lesional cells resemble LC. It has been hypothesized that the putative cells in LCH may arise from epidermal LC, dermal and lymphoid tissue resident dendritic cells or mononuclear phagocyte precursors.^[6] LCH is composed of three morphologically similar lesions: Hand-Schuller-Christian syndrome, Abt-Letterer-Siwe syndrome and Eosinophilic granuloma. A congenital self-healing form labeled Hashimoto–Pritzker disease has also been described. All these lesions exhibit proliferation of cells with characteristic Birbeck granules found in Langerhans cells. Hence differentiation between these entities has largely been abandoned to be replaced by a unified terminology – LCH.^[7,8]

LCH is considered a pediatric disease but may present at any age from the neonatal period to adult age. LCH can affect any organ, the most common sites being bone, skin, lymph nodes, ears, lungs and pituitary.^[8] The clinical course and prognosis of LCH is diverse ranging from a spontaneously regressing single lesion to a life – threatening extensive multi-system disorder with rapid progression and death. Based on the clinical course LCH may be classified into (1) restricted (single system) LCH or (2) extensive (multi system) LCH. Restricted LCH primarily involves the skin, bone or lymph nodes with or without diabetes insipidus whereas the extensive multi system form manifests visceral organ or hemopoietic system involvement with or without bone lesions, diabetes insipidus, adjacent lymphnode involvement and skin rash. The severity of the disease tends to be age related with extensive LCH seen in the very young.^[6]

The true nature of LCH has long been debated. Most forms of LCH consist of a clonal population of cells as shown by chromosome inactivation studies. Pulmonary LCH is an exception consisting of a non-clonal population of cells leading to speculation that it may be a reactive process.^[6] Evidence for a neoplastic etiology has been supported by the strong immunoreactivity of LCH cells for p53 and Ki-67 markers. Occurrence in monozygotic twins and a t (7, 12) translocation suggests that LCH may be an inherited genetic defect although the role of heredity in the transmission of the disease is unknown.^[6,9] Neonatal infections particularly Epstein–Barr virus infection, exposure to chemical solvents and a positive

family history of thyroid disease has been associated with an increased incidence of LCH. Thus, LCH may be regarded as a genetic disorder triggered by environmental agents.^[7,9]

Cutaneous lesions are very common in LCH. It is usually the first sign of the disease, being reported in 80% of cases and carries prime diagnostic significance.^[8] The classical cutaneous lesions of LCH have been described as scaly, erythematous, seborrhea-like eruptions of brown to red papules involving the face, scalp, trunk and are particularly pronounced in the intertriginous zones. Our case was an 8 month old asymptomatic female infant with a positive history of occasional rashes on the scalp and trunk that was overlooked due to the erratic presentation of the lesions. Newborns present with a wide array of skin lesions, which may often be mistaken for an infectious process. In our case, a skin biopsy with immunohistochemical evaluation would have confirmed the diagnosis of LCH. Therefore, we recommend that these varied skin lesions in infants be viewed with a great deal of suspicion.

Our case presented with an ulcerative growth in the upper right alveolus. Radiographs suggested a possible cystic lesion while CT imaging of the head and neck revealed the destructive nature of the lesion. The characteristic clinical manifestations in LCH are fever, anemia, thrombocytopenia, hepatosplenomegaly and lymphadenopathy.^[8] In our case the clinical and hematological findings were noncontributory but bilateral cervical lymphadenopathy was observed on CT imaging. Findings at the time of biopsy also suggested an aggressive lesion.

The diagnosis of LCH is based on hematologic and histologic criteria established by the International Histiocyte Society in 1987.^[6] All suspected cases require confirmatory biopsy and an accurate assessment of the extent of the disease.^[10] The LCH cell irrespective of the site of the lesion is characterized by the expression of CD1a and CD207/Langerin which can be easily detected by conventional immunohistochemistry. Besides these two markers, additional markers like CD14, CD68 and S100 are used for co-staining the lesional cells.^[6,7] In our case, a final diagnosis of LCH was based on the histopathological findings and immunohistochemical staining of the lesional cells by CD1a and S-100 protein. Previously the gold standard for diagnosis of LCH was the demonstration of Birbeck granules by electron microscope, but this has been replaced by detection of Langerin or CD1a expression in the lesional cells.^[11] Once the diagnosis of LCH was established, it was suggested to the consulting dentist that a thorough physical examination with attention to examination of lymph nodes and abdominal organs be performed to rule out multisystem LCH.

Treatment modalities for LCH should be designed based on the site and extent of involvement. The restricted form of the disease is treated minimally as a biopsy to establish the diagnosis may by itself lead to the resolution of the disease.

Therapy is often unnecessary for patients with cutaneous LCH but very young children should be carefully monitored to determine the progression to an advanced disease. Local or systemic corticosteroids are the first line of therapy in mild forms of cutaneous LCH while the more severe forms may need mild chemotherapy. Treatment for single bony lesions is localized to the affected site while treatment of multisystem LCH is aimed at improving survival, preventing diabetes insipidus and other late complications that may arise due to the therapy or disease. Studies have proved that initial therapy with minimal toxic chemotherapy significantly improved survival in patients with multisystem LCH and organ dysfunction particularly in children.^[6]

Our case was a multisystem high-risk case who succumbed to her disease in spite of the chemotherapy. The poor response to treatment in our case may be attributed to the delay in seeking treatment.

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