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CASE REPORT

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Oral mucosal involvement in Langerhans' cell histiocytosis: long-term follow-up of a rare case

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ABSTRACT

Langerhans' cell histiocytosis (LCH) is a rare disease where different organs and systems may be affected. Oral involvement generally consists of mucosal ulceration associated with lesions of the underlying bone. Many reports exist about the misdiagnosis of this disease. Various symptoms may lead the clinician to an incorrect diagnosis, especially with multiple organ involvement. Oral manifestations are common, and dentists should be aware of this disease and evaluate intraoral findings accordingly. This study presents an LCH case characterized by oral mucosal ulcerations with no involvement of the underlying bone. A definitive diagnosis was made by open biopsy from the oral mucosa.

Keywords: Langerhans' cell histiocytosis, oral ulcer, oral diagnosis.

Abbreviations and acronyms: DI = diabetes insipidus; LCH = Langerhans' cell histiocytosis; MRI = magnetic resonance imaging.

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INTRODUCTION

Langerhans' cell histiocytosis (LCH) is a rare disease that can occur at any age and is characterized by local proliferation of disseminated forms of dendritic Langerhans' cells.[1] LCH has been historically classified into three clinical variants: eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease.[2] These diseases are collectively grouped under the term LCH (formerly known as histiocytosis X) because of the involvement of Langerhans' cells.

Different organs and systems may be affected in LCH, such as the lungs, liver, lymph nodes, spleen, haematopoietic tissue and mucocutaneous tissues. However, bone is the tissue most frequently affected. The majority of patients present with solitary or multiple bone lesions, and involvement of the jaws (particularly the mandible) is not unusual.[3] In oral mucosal involvement, mucosal ulceration is typically associated with lesions of the underlying bone.[4] LCH is known to mimic many other conditions. Its diagnosis is especially difficult due to its wide clinical spectrum, ranging from a single lesion to a multi-system disorder. There are many reports about the misdiagnosis of this disease.[5–8] Oral manifestations are common, and dentists should be aware of the symptoms of the disease and make proper assessments. Performing laboratory work-up with clinical and radiological assessment for the accurate diagnosis of oral mucosal conditions is essential.

This study presents an LCH case characterized by oral mucosal ulcerations with no involvement of the underlying bone. A definitive diagnosis was made by open biopsy from the oral mucosa. LCH had not been diagnosed by previous methods and therefore the patient had received incorrect treatment. Because the oral cavity is one of the first systems affected by LCH, it is important for the dentist to be able to recognize oral lesions, make the pathological examination and ensure appropriate treatment management.

CASE REPORT

A 41-year-old female patient was referred to our clinic in September 2007 with a complaint of bilateral palatal ulcerations of three months duration. There was no pain or bleeding, but she occasionally experienced a burning sensation on the ulcerated areas. The patient had been previously evaluated by two different dentists and told that the lesions occurred due to her depleted immune system following an influenza infection. She was given antibiotics but the lesions did not improve. She was also experiencing

knee pain and seeking treatment at a physical therapy department.

Her past medical history indicated that symptoms of polyuria and polydipsia had developed in July 2004, and diabetes insipidus (DI) was diagnosed. She gave birth to her last child one year before her admission to the endocrinology department, and had amenorrhoea in the postpartum period after one menstrual period. Pituitary magnetic resonance imaging (MRI) showed a thickened distal pituitary stalk and a mildly widened optic chiasm. Spontaneous hyperintensity of the neurohypophysis was lost. Based on clinical and laboratory findings, imaging studies, and her DI history, she was diagnosed with lymphocytic hypophysitis and was started on desmopressin acetate. The patient was being monitored for the DI and hypophysitis, and continued to receive replacement therapy for pituitary failure until she was referred to the oral and maxillofacial surgery department where an accurate diagnosis was made by biopsy from the oral mucosa.

In our department, a clinical examination showed bilateral ulcerations of the hard palate adjacent to the teeth, between the second premolar and third molar on the right side, and adjacent to the third molar on left side (Figs 1 and 2). The lesions had non-indurated, irregular margins. Radiographic investigation showed no pathosis of related bone or periodontium (Fig 3). An open biopsy from the oral mucosa was performed under local anaesthesia, and microscopic findings showed histiocytic cells and eosinophil leukocytes below the squamous epithelium (Fig 4). The biopsy revealed the presence of LCH.

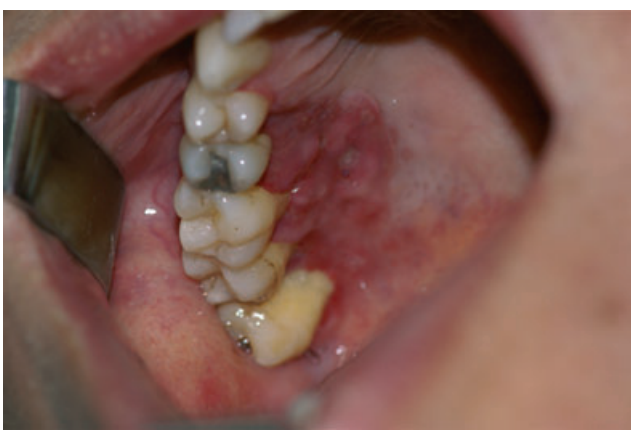

Fig 1. Non-indurated, irregular ulcerations on the right side of the hard palate.

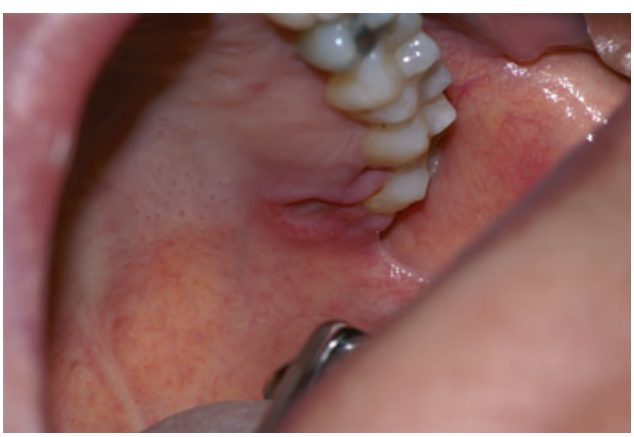

Fig 2. Non-indurated, irregular ulcerations on the left side of the hard palate.

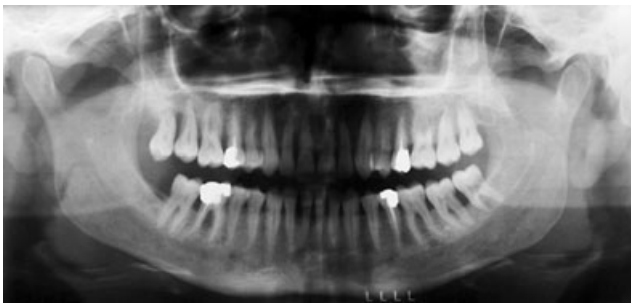

Fig 3. Panoramic radiograph shows there is no pathosis of the related bone.

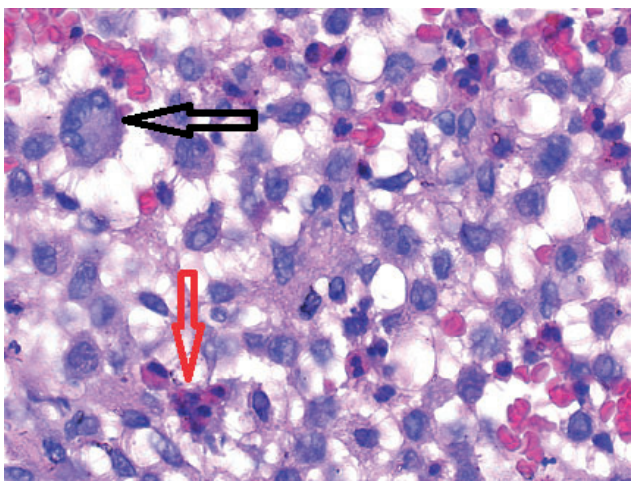

Fig 4. Eosinophilic granuloma, characterized by diffuse infiltration of histiocytic cells (black arrow) and eosinophilic leukocytes (red arrow). H&E ×400.

At the same time, the patient was admitted to the Physical Medicine and Rehabilitation Center with a complaint of knee pain. Radiography revealed a 1 cm lytic lesion on the left side of the ischium pubis, lytic lesions on the distal diaphyses of both femurs, and irregularity in the cortical bone. The patient's clinical and radiologic findings were evaluated, and because of multiple organ involvement, it was decided to start a 35-week chemotherapy regimen with alternating vinblastine-prednisolone and methotrexate every week, with daily mercaptopurine.

In the 21st week of treatment, the patient reported that her knee pain had completely resolved. Scintigraphy showed minor improvements in the lytic lesions, but her clinical status had improved. Oral lesions disappeared after 35 weeks, and her follow-up in November 2010 showed no recurrence (Figs 5 and 6).

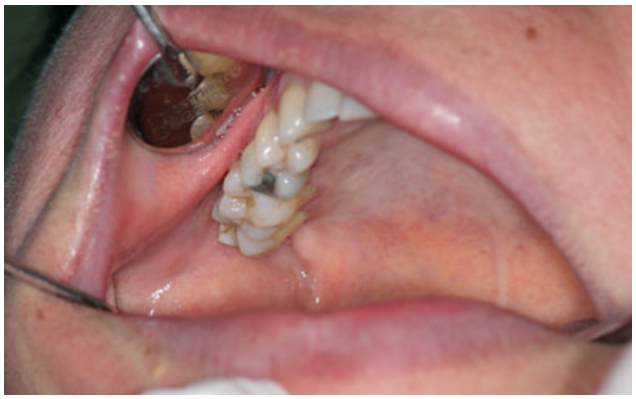

Fig 5. Photograph taken in November 2010 shows no recurrence on the right side of the hard palate.

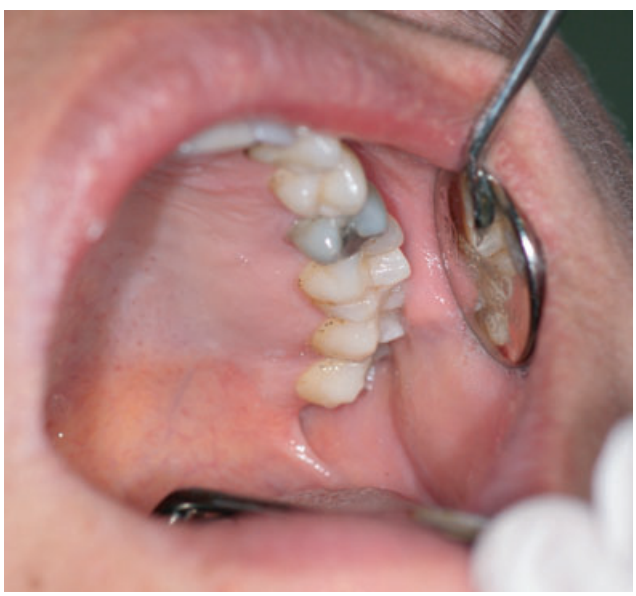

Fig 6. Uneventful healing of the left side of the hard palate.

DISCUSSION

LCH is a reactive condition in which cells with the Langerhans' phenotype accumulate in various tissues and organs and cause damage. Although the disease has been known for about a century, its aetiology remains largely unknown. In the literature, various aetiopathologic mechanisms have been proposed. Many investigators view the disease as a reactive process rather than as a neoplasm,[9] whereas studies examining the clonality of the lesional cells of this condition have shown it to be a monoclonal proliferation, a finding more consistent with a neoplastic process.[9,10] Genetic instability may lead to histiocytic proliferation and disease progression[11] but due to the lack of studies on this subject, no acceptable hypothesis supporting genetic abnormalities has been proposed. The exact pathogenesis remains unclear; it is likely that the aetiology is multifactorial.

LCH patients show different symptoms for different disease manifestations. Because the disease affects multiple organ systems, symptoms may confuse the physician and the underlying systemic cause may be overlooked. In the literature, there are many reports of misdiagnoses of LCH. Chen and Peron[5] reported a case of eosinophilic granuloma falsely diagnosed as a radicular cyst in a 28-year-old patient. A diagnosis of silicosis was made after radiological evaluation of a patient who had been professionally exposed to silica dust.[6] After follow-up for 12 years without significant modification of the X-ray or respiratory functions, the patient died of a ruptured aortic aneurysm. At autopsy, examination of the lungs resulted in exclusion of the initial diagnosis of silicosis, and concluded the presence of histiocytosis X. A destructive lesion in the diaphysis of the right femur in a 9-year-old boy was wrongly diagnosed as Ewing's sarcoma on the basis of the radiological findings and a fine needle aspiration cytology report.[7] An open biopsy of the lesion revealed a histopathological picture of eosinophilic granuloma. It is important to perform an open biopsy and laboratory work-up to obtain a definitive diagnosis. In the cases of suspicious oral lesions, physicians should not hesitate to undertake pathological and histological examination. In the LCH case presented here, until oral symptoms developed and a biopsy was performed, the patient was incorrectly diagnosed as having lymphocytic hypophysitis and given inappropriate treatment.

In 2006, Zhang *et al.*[8] reported their experience of 44 LCH patients treated from January 1990 to December 2003. Twenty-six were misdiagnosed with dermatosis, six with haemopathy, seven with lung tuberculosis, two with DI, two with ear or eye disease, and six with bronchopneumonia. The conclusion was that pathological examination is helpful for early diagnosis, treatment, and prevention of severe complications. Our patient's past medical history included neck pain on the left side one year after she gave birth to her child in 2003. After clinical examination and MRI, the patient was diagnosed with lymphocytic hypophysitis and pituitary replacement therapy was given. Pituitary insufficiency after giving birth is one of the differential diagnoses of lymphocytic hypophysitis, and because of this common knowledge, the systemic situation was overlooked by the physician. Clinicians dealing with maxillofacial and head and neck disorders must be aware of the possibilities for diagnosing LCH and the subsequent spectrum of clinical presentations.

In LCH, gingival lesions are generally associated with adjacent bone involvement and loosening of neighbouring teeth; infection may result.[12,13] Zuendel *et al.* claimed that swelling and ulceration of the gingiva may develop if the disease breaks out of the bone.[14] Nakamura *et al.* presented a case of LCH in which they observed osteolytic bone areas associated with the teeth.[15] They reported that maxillary and mandibular lesions are frequently present and appear as solitary or

multiple radiolucent lesions. In contrast, in our case, we radiologically confirmed no bone involvement with oral ulceration. Although oral involvement of LCH usually manifests as a gingival swelling or ulceration resulting from an underlying bone lesion, non-bone related cases have been reported.[4,13,16–18] To our knowledge, this is the sixth report in the dental literature of non-bone related oral ulcerations in an LCH patient.

Various treatment modalities for LCH have been proposed, including close observation, surgical curettage, local injection of corticosteroids, low-dose radiotherapy, high-dose systemic corticosteroids, chemotherapy and, for more resistant cases, bone marrow transplantation and antibody therapy.[19] The general opinion is to determine the therapeutic regime based on the disease severity and number of systems involved.

In single system diseases, local currettage or surgical excisions are the most preferred treatment alternatives for solitary bone lesions. Painful bone lesions may require intralesional steroid injection, such as prednisone or, rarely, radiation therapy. In cases with severe cutaneous involvement, topical nitrogen mustard may be used.[20] Treatment resistant sites may require systemic chemotherapy. In multiple organ involvement, systemic chemotherapy is indicated. Low to moderate doses of methotrexate, prednisone and vinblastine have been used successfully.[20,21] This treatment scheme was used for our patient. The patient's clinical symptoms rapidly disappeared during the 35-week chemotherapy regimen, and oral lesions healed completely. The patient continues to be monitored, and there has been no systemic complaint or clinical recurrence.

CONCLUSIONS

Oral lesions can be a sign of systemic disease. Clinicians dealing with the maxillofacial area should be aware of the oral symptoms of systemic disease and the clinical findings, and verify the diagnosis by biopsy if necessary. In the LCH case presented here, although the ulcerated areas were not associated with the underlying bone, clinicians suspected underlying bone involvement when considering the clinical findings. A definitive diagnosis was achieved with an open biopsy from the oral mucosa.

REFERENCES

1. Ardekian L, Peled M, Rosen D, Rachmiel A, Abu el-Naaj I, Laufer D. Clinical and radiographic features of eosinophilic granuloma in the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:238–242.
2. Piattelli A, Paolantonio M. Eosinophilic granuloma of the mandible involving the periodontal tissues. A case report. J Periodontol 1995;66:731–736.
3. Milián A, Bagán JV, Basterra J, Jimenez Y, Lloria E. [Oral histiocytosis X with severe upper maxillary destruction.] Acta Otorrinolaringol Esp 1996;47:475–478.
4. Cleveland DB, Goldberg KM, Greenspan JS, Seitz TE, Miller AS. Langerhans' cell histiocytosis. Report of three cases with unusual oral soft tissue involvement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:541–548.
5. Chen N, Peron JM. The nonhealing of the buccal mucosa after tooth extraction. Apropos a case of histiocytosis X. Rev Stomatol Chir Maxillofac 2000;101:33–35.
6. Weber-Chappuis K, Thorens B. Histiocytosis X falsely diagnosed as silicosis. Rev Med Suisse Romande 1997;117:901–905.
7. Biswal BM, Lal P, Uppal R, Mallik S. Unifocal Langerhans' cell histiocytosis (eosinophilic granuloma) resembling Ewing's sarcoma. Australas Radiol 1994;38:313–314.
8. Zhang K, Zeng H, Chen WQ. Clinical features and diagnosis of Langerhans cell hyperplasia. Ai Zheng 2006;25:88–91.
9. Granda FM, McDaniel RK. Multiple progressive eosinophilic granuloma of the jaws. J Oral Maxillofac Surg 1982;40:174–178.
10. Graaf JH, Egeler RM. New insights into pathogenesis of Langerhans' cell histiocytosis. Curr Opin Pediatr 1997;9:46–50.
11. Hanapiah F, Yaacob H, Ghani KS, Hussin AS. Histiocytosis X: evidence for a genetic etiology. J Nihon Univ Sch Dent 1993;35:171–174.
12. Baumgartner I, Von Hochstetter A, Baumert B, Luetolf U, Follath F. Langerhans cell histiocytosis in adults. Med Pediatr Oncol 1997;28:9–14.
13. Milian MA, Bagan JV, Jimenez Y, Perez A, Scully C, Antoniades D. Langerhans cell histiocytosis restricted to oral mucosa. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:76–79.
14. Zuendel MT, Bowers DF, Kramer RN. Recurrent histiocytosis X with mandibular lesions. Oral Surg Oral Med Oral Pathol 1984;58:420–423.
15. Nakamura S, Bessho K, Nakao K, Iizuka T, Scott RF. Langerhans' cell histiocytosis confined to the jaw. J Oral Maxillofac Surg 2005;63:989–995.
16. Bottomley WK, Gabriel SA, Corio RL, Jacobson RJ, Rothchild N. Histiocytosis X: report of an oral soft tissue lesion without bony involvement. Oral Surg Oral Med Oral Pathol 1987;63:228–231.
17. Finney DS, Rees TD, Wright JM, Blanton PL. Solitary eosinophilic granuloma (histiocytosis X) of the gingiva. A report of two cases. J Periodontol 1988;59:457–460.
18. Hashimoto K, Takahashi S, Fligiel A, Savoy B. Eosinophilic granuloma. Presence of OKT6-positive cells and good response to intralesional steroid. Arch Dermatol 1985;121:770–774.
19. Levy J, Monos T, Kapelushnik J, Maor E, Nash M, Lifshitz T. Ophthalmic manifestation in Langerhans cell histiocytosis. Isr Med Assoc J 2004;6:553–555.
20. Das JK, Soibam R, Tiwary BK, Magdalene D, Paul SB, Bhuyan C. Orbital manifestations of Langerhans cell histiocytosis: a report of three cases. Oman J Ophthalmol 2009;2:137–140.
21. Arico M, Girschikofsky M, Généreau T, *et al.* Langerhans cell histiocytosis in adults: report from the International Registry of the Histiocyte Society. Eur J Cancer 2003;39:2341–2348.

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