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Langerhans cell histiocytosis in a child: a 10-year follow-up

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Background. This report describes a case of the benign form of Langerhans cell histiocytosis, which involves only the maxilla and mandible, and has no extraskeletal manifestations.

Case report. A 2.9-year-old boy was referred to a paediatric dentistry clinic, where clinical, radiographic and histological findings were found to be consistent with Langerhans cell histiocytosis. The difficulties involved in the diagnosis and the subject's functional oral rehabilitation are described. In view of the presence of large bone lesions, systematic treatment consisted of oral chemotherapy and the administration of methylprednisolone by intralesional infiltration. Oral examination revealed complete resolution of the ulcerative lesions. The soft tissue appeared healthy and had a normal colour. There was no tooth mobility and radiography provided evidence of bony healing.

Conclusion. This case is particularly interesting because follow-up clinical and radiographic observations have been made over the past 10 years. The successful treatment had several objectives, including providing the patient with an aesthetic appearance and recovering the lost vertical dimension of occlusion.

Introduction

In 1953, Lichtenstein[1] suggested that the term histiocytosis X should be used to describe a group of three disorders, including eosinophilic granuloma, Letterer–Siwe disease and Hand–Schüller–Christian disease. He proposed that these disorders were different manifestations of a single pathological process since they had common histological features of unknown origin. Later evidence suggested that the three diseases have an abnormal proliferation of histiocytic cells with characteristic Birbeck granules; therefore, differentiation between the three entities has been abandoned and the term Langerhans cell histiocytosis (LCH) is now commonly used[2].

As defined by the Writing Group of the Histiocyte Society[3], LCH develops in both childhood and adulthood, its clinical course and prognosis depending on the age of initial manifestation, as well as the number and sites of the organs involved. Prominent locations are the flat bones, such as the ribs, the spine and the base of skull.

The annual estimated incidence of LCH ranges from one per 200 000 to one per 2 million. Few cases of LCH were reported in a recent analysis of oral and maxillofacial pathologies found in children over a 30-year period[4]. The ratio of male:female incidence has been reported[5,6] to range from 2:1 to 4.6:1.

Oral lesions may be the earliest manifestation of the condition, and in many cases, the mouth may be the only site of involvement[7,8]. The incidence of oral manifestations of LCH has been reported to be as high as 77%[9]. In a report of a series of 50 patients, 36% had oral involvement and the dentist was the first to detect oral lesions in 16% of the cases[10]. Hartman[5] reported oral involvement of LCH in 10% of the cases in his study, and that the most common oral symptoms were jaw swelling or a palpable mass. Most of the subjects were male and the disease had appeared to start before the age of 10 years. The mandible was more involved than the maxilla and the posterior region was the predominant site[11].

The reason for the atypical proliferation of LCH still remains unclear. Besides the observation

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that patients with LCH do have certain immune compromises that are not the cause of the disease, there is no evidence why such a proliferation of Langerhans cells leading to tissue infiltration and destruction occurs[12]. According to Stoll *et al.*[13], a basic immune defect may lead to proliferation of Langerhans cells or the Langerhans cell itself may carry a genetic defect leading to abnormal cellular proliferation. Bathia *et al.*[14] conducted an epidemiological study of Langerhans cell histiocytosis in children and reported an increased incidence of the disease in conjunction with neonatal infections, exposure to chemical solvents and a positive family history of thyroid disease.

The leading clinical symptom of LCH within the mandibular and maxillary bones is pain, which is sometimes misdiagnosed as a marginal periodontal infection[12]. Apart from such local complaints, the disease is rather symptomless, although some patients complain about loosening of teeth. Other symptoms can be necrotizing and ulcerating defects of the mucosa, and swelling of the jaw[15].

Radiologically, LCH presents as localized, punched-out radiolucencies with no calcification and no sign of sclerosis or reaction at the borders. There may be severe alveolar bone resorption, producing the appearance of teeth 'floating in space'[12]. The radiographic findings of the lesion must be based on bone erosions, marginal changes, periosteal reactions, effects on teeth and pathological fractures[16].

Clinically, LCH is difficult to distinguish from bone metastasis, osteomyelitis or even malignant tumours. Only by histology can the final diagnosis of LCH be made[12].

Morphologically, the cells are characterized by lobulated basophilic nuclei and eosinophilic cytoplasm. By immunohistochemistry, tumour cells usually express S-100 and CD1a. The detection of cytoplasmic inclusion bodies known as Birbeck–Breatnach granules is a typical characteristic of LCH[12]. It is also possible to verify local proliferation of LCH by the antigen Ki-67. Although Bartnick *et al.*[11] felt that the number of antigen-Ki-67-positive cells was related to the disease activity, it was not possible to make a definitive statement because of the small number of patients in the sample.

Besides histopathological diagnosis, bone scintigraphy is mandatory to exclude or to detect additional bone lesions. A common extraosseous manifestation can be found in the lungs, and the clinical symptoms may be present as coughing or dyspnoea[12].

While a therapeutic protocol does not exist, there are many possible combinations of surgery, chemotherapy and radiation. In addition to these therapeutic combinations, possible treatments include intralesional steroid injection, interferon or cyclosporin A-injections, and bone marrow transplantation[11]. New therapeutic strategies are represented by monoclonal CD1a-antibody therapy and gene transfer into haemopoietic progenitor cells[12].

Case report

A 2.9-year-old boy was referred by his general dental practitioner to the Department of Child Dental Health at the Centre for Odontological Research (CPO), São Leopoldo Mandic Dental Research Institute, Campinas, São Paulo, Brazil. The dentist had expressed concern regarding the mobility of the lower anterior and posterior teeth. The boy's parents stated that the gingiva of their son had begun bleeding about 3 months before presentation to the dentist.

At the time of examination, the patient had good general health, with no abnormal extraoral signs and was generally comfortable.

Intraoral examination revealed both tooth mobility, and gingival tissue that had a granular texture and bled easily. The adjacent mucosa and other oral tissues appeared to be within normal limits. The lesion had a periodontal involvement, and had caused damage to the contour of the alveolar ridge of the mandible, extending from the distal surface of the first left primary molar to the distal surface of the left canine (Fig. 1), and from the mesial surface of the right central incisor to the distal surface of the right primary canine (Fig. 2). At the maxilla, the lesion appeared as a single, irregularly shaped nodule, which was sharply demarcated, approximately 3 cm in diameter and reddish in colour, and there was evidence of bone resorption on the first and second left primary molars (Fig. 3). It was noted that the subject had a healthy primary dentition and exhibited gross plaque deposits.

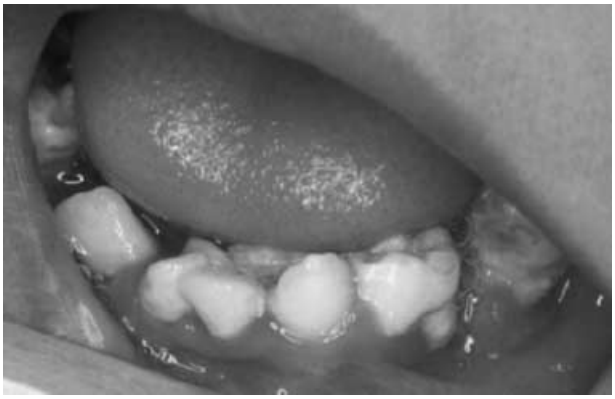

Fig. 1. Clinical appearance of the mouth of a patient suffering from Langerhans cell histiocytosis. Note the gingival tissue with a granular texture that bleeds easily.

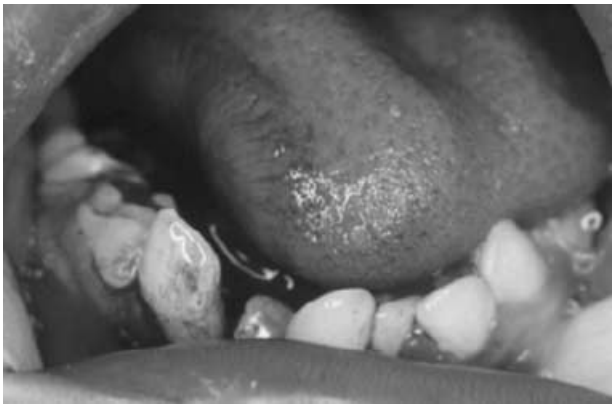

Fig. 2. Clinical appearance at presentation. Note the almost complete bone loss around the primary canine on the right side of the mandible.

A panoramic radiograph revealed the presence of a huge radiolucent, circumscribed and sharp unilocular image on both sides of the mandible, extending from the mesial surface of the second left primary molar to the mesial surface of the left central incisor, and from the mesial surface of the right central incisor to the distal surface of the right primary canine. This had not caused an expansion of the buccal and lingual cortical plates, but had caused a displacement of the germs of the anterior permanent lower teeth (Fig. 4). There was also severe alveolar bone resorption, producing the appearance of teeth 'floating in space' in the area of the alveolar bone on the left side of the mandible.

A biopsy made by incision was subsequently carried out and the material was sent for histopathological examination at the Department of Oral Pathology of the CPO São Leopoldo Mandic Dental School.

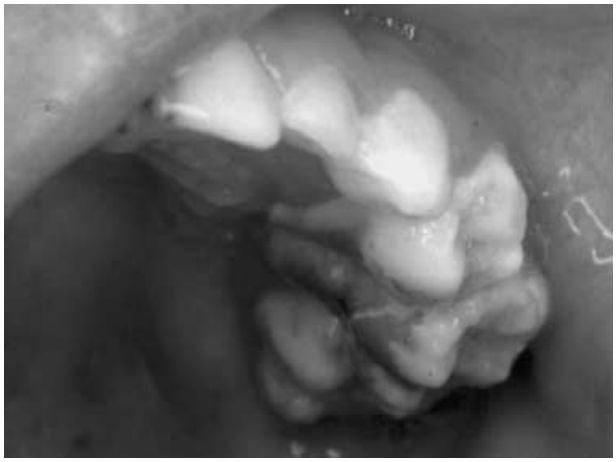

Fig. 3. Clinical appearance of an ulcerative lesion on the hard palate.

The histological characteristics of the biopsied specimen comprised histiocyte-like cells. In some fields, these cells presented multilobulated nuclei and prominent nucleoli. This predominant cell population was admixed with variable numbers of eosinophils and neutrophils. Focal areas of chronic inflammatory infiltrate and haemorrhagic exudates were also seen (Fig. 5). The biopsy specimen was submitted for imunohistochemical stains, and the main cell population was positive for S-100.

The clinical, radiographic and histological findings were consistent with LCH, and the disease was first identified by the dentist. These initial oral findings suggested that other areas of the body should be examined using scintigraphy and computed tomography. A skeletal survey was normal. The results of haematological investigations and urinalysis were within normal limits.

In view of the presence of large bone lesions, systematic treatment was considered to be necessary for a 6-month period. The treatment consisted of chemotherapy [induction therapy with VP16 (etoposide) and VBL (vinblastine), and maintenance therapy with MTX (methotrexate), VBL (vinblastine), VP16 (etoposide) and 6-MP (mercaptopurine)] and intralesional injection of methylpredinisolone acetate, as suggested by Cohen *et al.*[17], Jones *et al.*[18] and Ong & Lian[19].

The subject responded well to chemotherapy: there is radiographic evidence of bony healing of

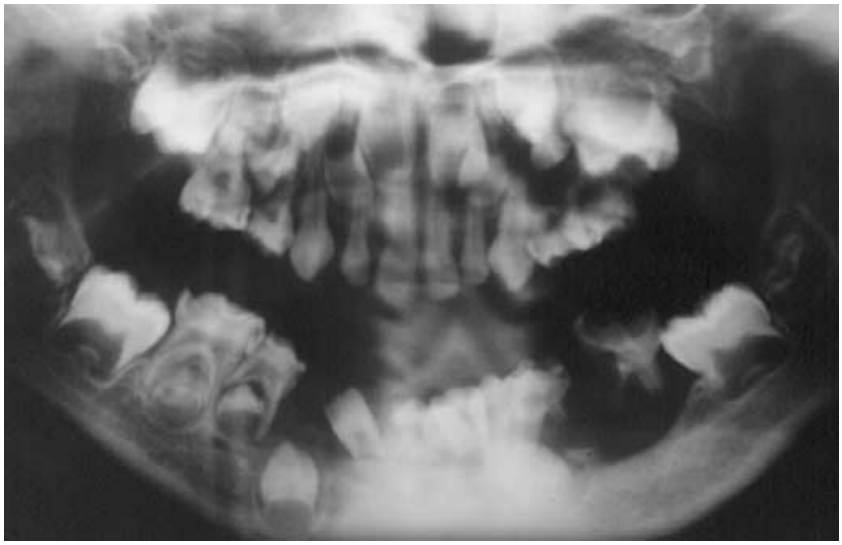

Fig. 4. Radiograph showing chronic disseminated Langerhans cell disease. Note the radiolucent lesions on both the left and right sides of the mandible.

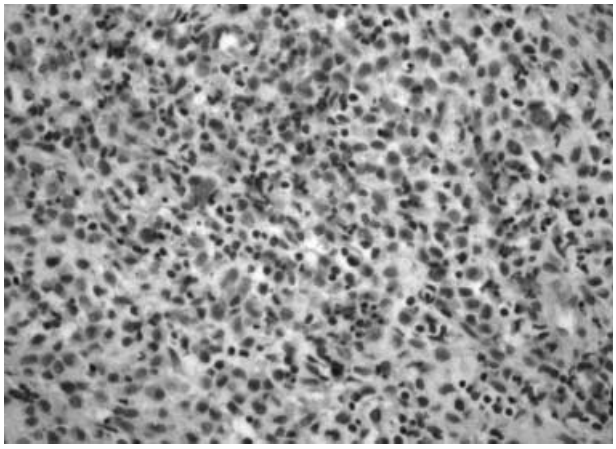

Fig. 5. Haematoxylin and eosin staining showing the typical histological picture of Langerhans cells histiocytosis, i.e. large cells with characteristically lobulated and indented nuclei, and faintly eosinophilic cytoplasm intermingled with a numerous eosinophils (original magnification ×40).

the left posterior maxilla, and both the right and left sides of mandible. Oral examination revealed complete resolution of the ulcerative lesions. The soft tissues appeared to be healthy and of normal colour. There was no tooth mobility.

Follow-up clinical and radiographic observations were made at 3 and 6 months, and one, 2, 5 and 10 years post-treatment, and bone recovery and eruption of some of the permanent teeth involved in the lesion have been observed (Figs 6 & 7). Chemotherapy has not had any influence on the later development of the permanent teeth.

During the past 10 years, the patient has had some caries lesions that were treated in their early stages. Composite resin was the material used for the restorations. Partial prostheses have been used during the growth and development of the mandible since the subject was 4 years old. These prostheses were made with self-wring acrylic, and the subject was instructed to present once a week for a period of one month for inspection, as well as possible corrections and adjustments. The boy was very cooperative and demonstrated very good compliance. The main objectives of the prostheses were to provide the patient with an aesthetic appearance and recover the lost vertical dimension of occlusion (Fig. 8).

Discussion

The epidemiological and clinical aspects of the lesion presented by the subject of this report are in accordance with most of the cases reported in the literature[2–11]. Hartman[5] found that about 10% of cases involve oral tissues and over 80% affect males. Hard- and soft-tissue lesions are predominant, with the mandible most affected, usually in the posterior region.

The microscopical aspects of the lesion, which showed typical features of LCH and immunohistochemical positivity to S-100, confirmed this diagnosis. Immunohistochemistry has been employed as an ancillary tool for the confirmation of LCH, since the presence of Birbeck

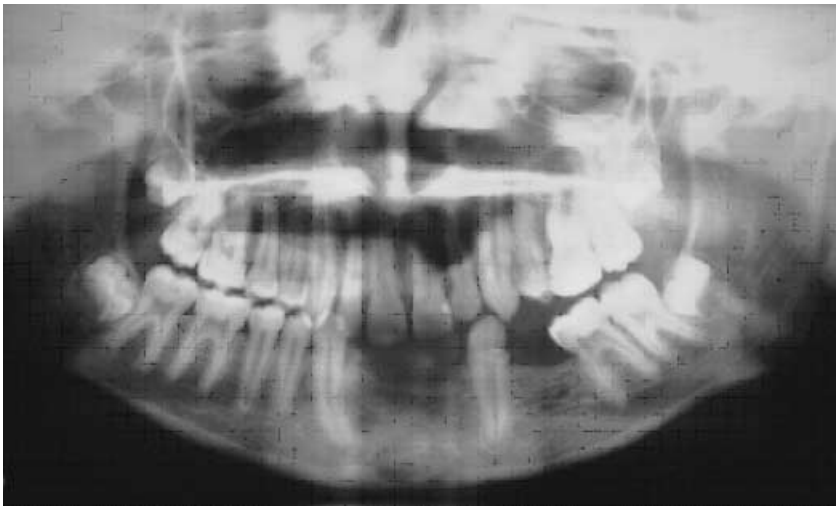

Fig. 6. Follow-up panoramic radiograph taken 10 years after the initial intervention.

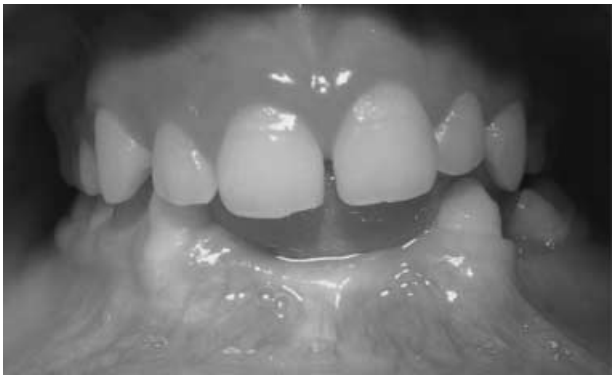

Fig. 7. Frontal view taken at follow-up approximately 10 years after the initial intervention.

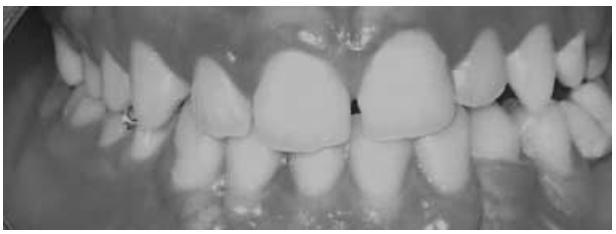

Fig. 8. Occlusion of the patient 10 years after the initial intervention.

granules in proliferating cells helps to distinguish the latter from other histiocytic lesions[20].

Treatment of this disease usually requires a multidisciplinary evaluation. After the diagnosis of eosinophilic granuloma was confirmed, a survey of the skeletal system was made, and the visceral system was also examined to verify the presence of lesions in other parts of the body; nothing was found.

In recent years, the pharmaceutical treatment of cases of LCH has become increasingly widespread. With regard to the unknown aetiology of the disease, most drug trials have, on the one hand, concentrated on immunosuppressant agents or immune modulators, and on cytostatic drugs on the other[12]. When this method has been studied further, it may provide a means of preserving the dentition when jaw lesions are encountered[21].

As the subject attended progressive follow-up appointments, the lesion appeared to resolve. It was noted that the lesion had reduced in size at the first review, a trend that continued over the following months, such that complete resolution occurred at 6 months. This was confirmed with routine radiography, which showed obvious signs of healing, such as a decrease in size demonstrated by the bony contours in the area previously occupied by the lesion and sclerosis, since the healing rate of bone lesions is very slow.

The treatment had several objectives, such as providing the subject with an aesthetic appearance at an early age to prevent psychological problems, recovering the lost vertical dimension of occlusion caused by tooth loss and avoiding interference with the eruption of the remaining permanent teeth. The establishment of preventive measures to improve the oral hygiene of this individual was also necessary.

The prognosis of this subject was initially very good, given his age at initial diagnosis, as well as the site and number of the structures

and organs involved[5,12]. According to Bartinick *et al.*[11], the prognosis of patients with the localized form of this disease is excellent. Nevertheless, LCH can be unpredictable and it is mandatory that all cases are subject to a careful follow-up programme, so as to identify any signs of local recurrence or dissemination. The potential for unifocal disease to become multifocal should be appreciated: it can occur within 6 months and usually affects children who are < 5 years of age[21]. The clinical prognosis of patients will become worse the larger the number of organs involved, the larger the number of organ dysfunctions, with rapid disease progression, with limited treatment response, and the younger the age of the individual when the disease first manifests itself[12].

Until the aetiology of LCH is better understood and definitive treatment programmes are developed, the most beneficial factors for patient care are, as in this case, early detection of the disease and appropriate referral[21].

What this paper adds

- This case illustrates the difficulties involved in the diagnosis of Langerhans cell histiocytosis and the results of treatment for this condition.

Why this paper is important to paediatric dentists

- This case report demonstrates the contribution of the dental team to the functional rehabilitation of the patient.

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