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Case Report

Surgical management of recurrent oral manifestation of Langerhans Cell Histiocytosis: case report

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Abstract

Langerhans Cell Histiocytosis (LCH) is a rare disease characterized by the abnormal proliferation of Langerhans cells, which can affect several tissues, including the oral cavity. This case report details the follow-up and treatment over 10 years of multiple recurrences. A 21-year-old female patient presented with tooth mobility and an osteolytic lesion in the mandible, diagnosed by incisional biopsy as LCH. Initially treated with surgical excision, the patient experienced a recurrence within less than a year and was subsequently managed conservatively with intralesional corticosteroid injection. However, conservative treatment was unsuccessful, and the patient underwent segmental resection of the mandible followed by bone fixation using plates and screws for reconstruction after a mandibular fracture. The patient later developed additional recurrences in other regions of the oral cavity, requiring further surgical interventions, along with systemic manifestations, which required chemotherapy for management. This case report shows the complexity of treatment and the importance of monitoring individuals with LCH by a multidisciplinary team.

Keywords: Langerhans cell histiocytosis; Oral manifestations; Oral surgery; Recurrence; Case report.

Statement of Clinical Significance

Langerhans Cell Histiocytosis is a rare disease with variable progression and systemic potential. This case report emphasizes the complexity of treatment, recurrence risks, and the need for rigorous monitoring and multidisciplinary care, especially in cases with systemic involvement.

Introduction

Langerhans Cell Histiocytosis (LCH), formerly known by the obsolete term "histiocytosis x", is a rare disease characterized by the exacerbated proliferation and accumulation of histiocytes (Langerhans cells), derived from bone marrow, in various tissues[1,2]. The etiology of LCH is not fully understood yet. Neoplastic stimuli, immune system dysfunction, genetic factors and inflammatory, bacterial or viral origin are believed to be potential causal factors[3,4,5,6].

Oral manifestation of LCH occurs in approximately 77% of cases and may present as multiple or single lesions[7]. The main manifestations most commonly include ulcerated lesions in the mucosa, lymphadenopathies and periodontal lesions. However, signs such as gingival inflammation, bleeding, gingival recession, necrosis, tooth mobility and premature tooth loss may also be observed[8,9]. The diagnosis is confirmed by the combination of clinical, radiographic and histopathological findings[8]. Histopathological examination shows a proliferation of cells with clear or eosinophilic cytoplasm with oval nuclei (Langherans cells), which are positive for CD1a and CD207, interspersed with a mixed inflammatory infiltrate. It is also possible to observe, in electron microscopy, racket-shaped cytoplasmic structures, known as Birbeck granules[8].

The treatment of LCH varies according to the location and extent of the lesion, and sometimes several therapeutic approaches are necessary due to changes in the

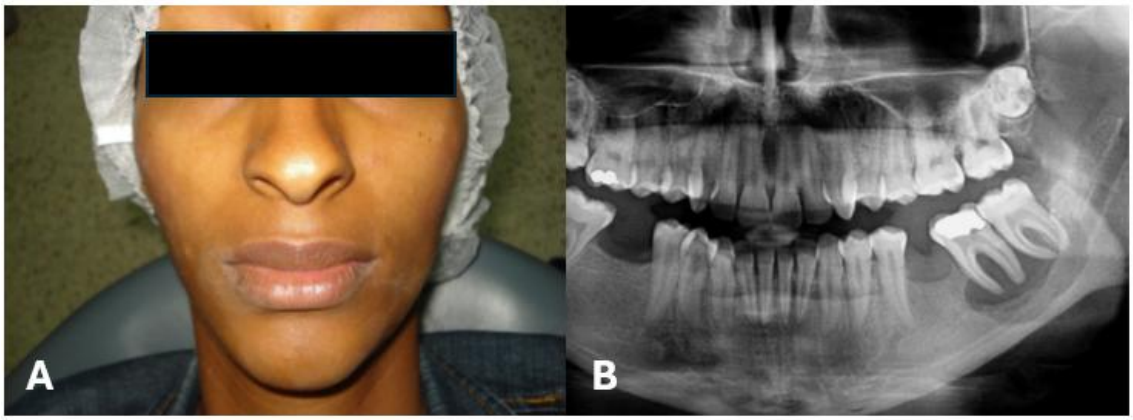
behavior of the disease[8,10]. Therapeutic modalities such as curettage, local infiltration of corticosteroids, radiotherapy and chemotherapy are described[10-13]. Despite the challenging clinical course, the prognosis of LCH is good, with a 5-year survival rate ranging from 75% to 100%, depending on the site of disease involvement[8].

The present study reports a case of LCH in an adult, with multiple oral and systemic manifestations, indicating the importance of the dentist's role in the diagnosis, treatment and monitoring of oral lesions of LCH.

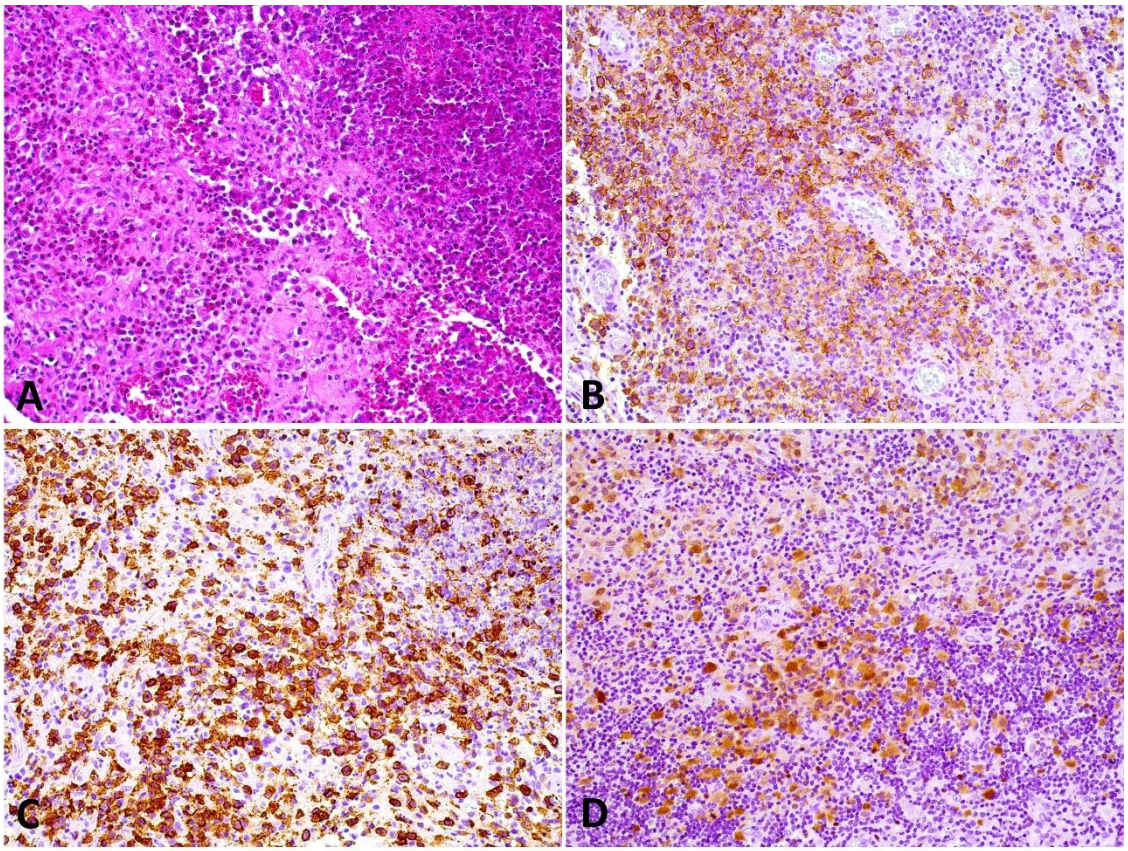
Case report

The reported case was collected from the Metropolitan Hospital Odilon Behrens (HMOB). Clinical information, radiographic findings, treatment, and follow-up were reviewed from the patient's medical records. Written informed consent was obtained through a signed informed consent form, and the present study was submitted to and approved by the HMOB Research Ethics Committee under protocol number 61493416.4.0000.5129.

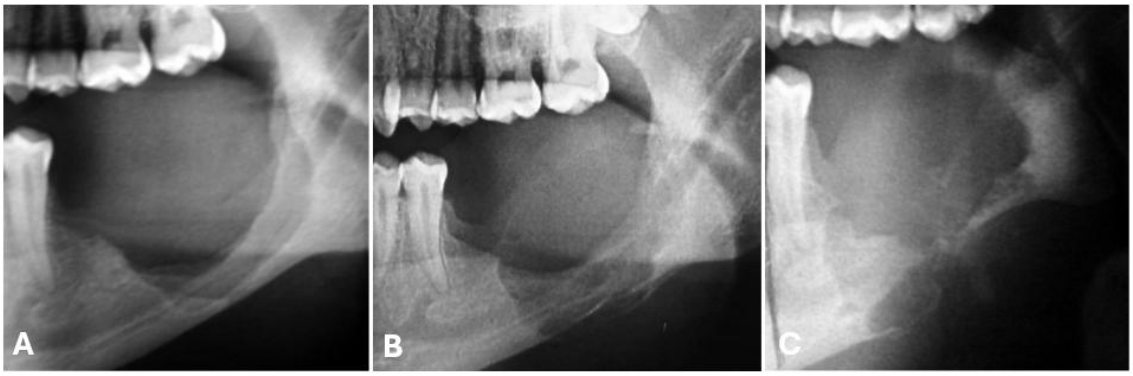
The 21-year-old female patient was first admitted to the stomatology clinic of HMOB in April 2012 for the evaluation of gingival swelling, ulceration and tooth mobility in the left posterior mandible. The extraoral clinical examination showed slight asymmetry in the lower third of the face (**figure 1-A**).



The radiographic examination showed a well-defined radiolucent lesion in the alveolar region, involving the roots of teeth 37 and 38, extending beyond the mandibular canal towards the base of the mandible (**figure 1-B**). The patient reported having previously sought dental care, where endodontic treatment of element 37 was unsuccessful, under the suspicion of a lesion of infectious origin. Considering the diagnostic hypotheses of LCH, tumor of odontogenic origin, central giant cell granuloma, and osteosarcoma, an incisional biopsy was performed. Histopathological examination revealed a proliferation of histiocytes with oval nuclei, sometimes lobulated, with fine chromatin and scarce cytoplasm, in addition to an intense inflammatory infiltrate consisting mainly of eosinophils and lymphocytes (**figure 2-A**).



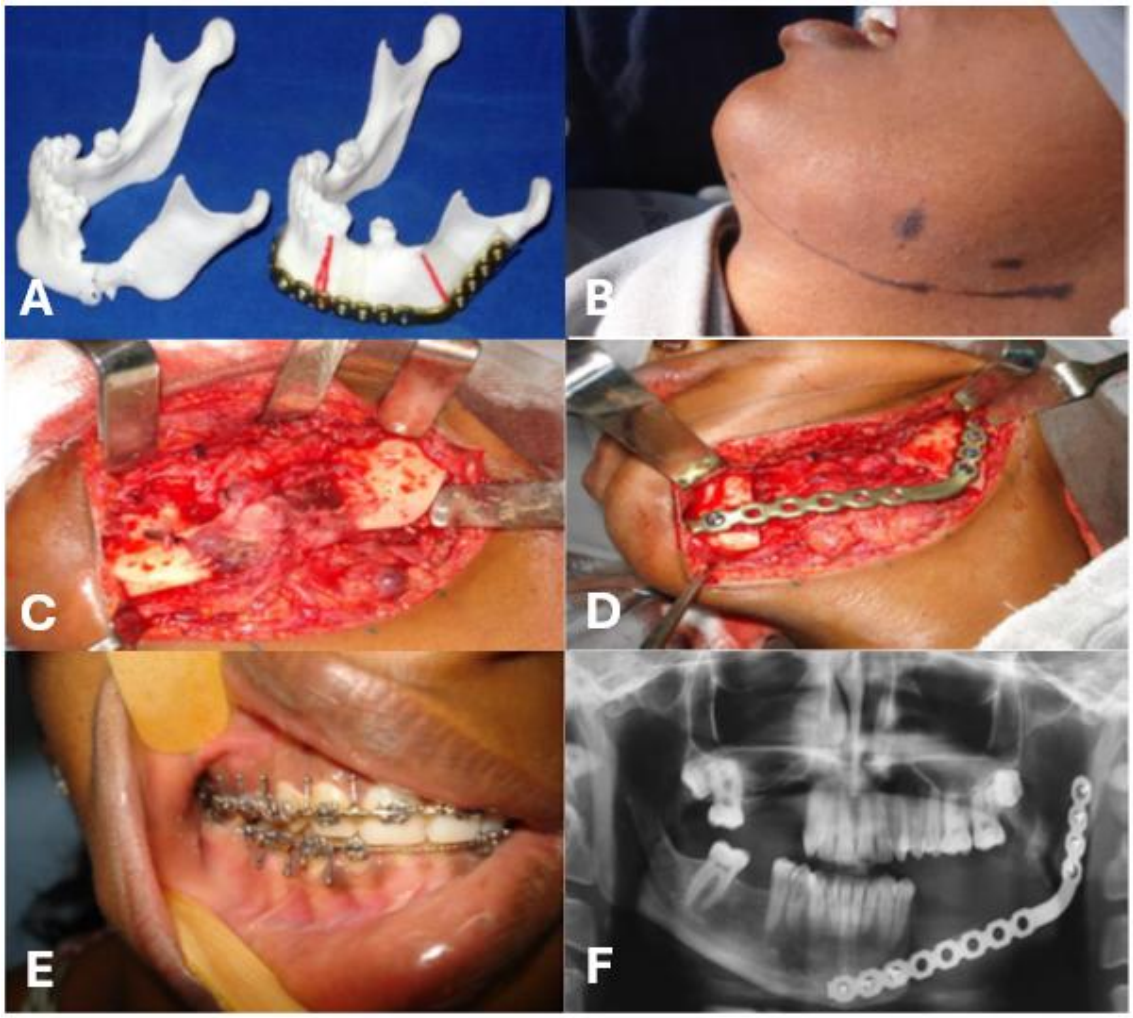
Immunohistochemical examination was then performed, which revealed positivity for CD1a (**figure 2-B**), CD207 (**figure 2-C**) and S100 (**figure 2-D**) proteins. Given these findings, the final diagnosis was Langerhans cell histiocytosis. Surgical excision of the lesion and removal of the involved teeth were performed (**figure 3-A**).



Systemic evaluation showed no signs of disseminated disease.

After 6 months postoperatively, a panoramic radiograph revealed an increase in the radiolucent area in the previously operated region, with a multilocular appearance and

extending from the postoperative region to the base of the mandible (**figure 3-B**). A new incisional biopsy of the affected area of the mandible was performed and confirmed the recurrence of LCH. Conservative treatment with intralesional corticosteroids was initiated in order to preserve the structures involved and avoid further morbidity to the patient. However, one month after the second injection, the patient developed a pathological fracture of the mandible due to proliferation of the lesion (**figure 3-C**). Surgical resection of the affected mandibular segment and reconstruction with a titanium plate were performed (**figures 4-A to 4-D**).



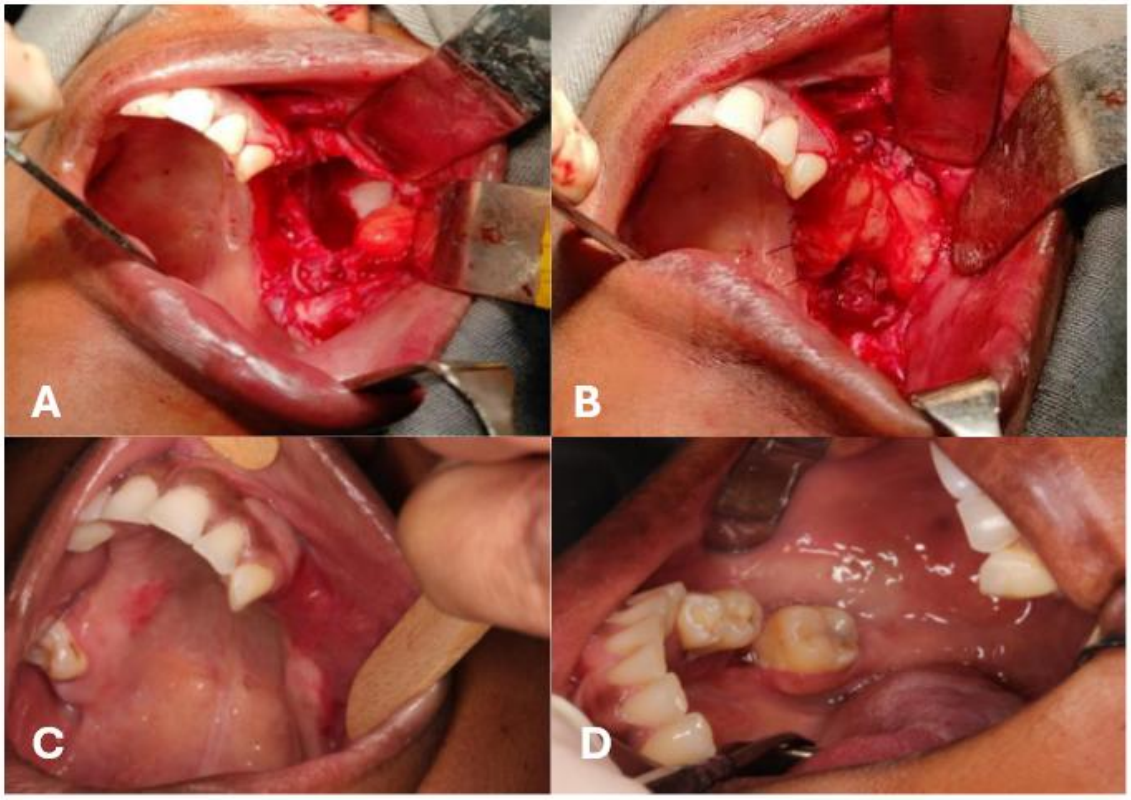
At the postoperative follow-up, the contralateral occlusion was checked and proved to be stable in maximum habitual intercuspation (**figure 4-E**), and the panoramic radiograph

revealed the postoperative appearance with plates and screws of the 2.4 system in the correct position (**figure 4-F**).

Nine months later, an intraoral examination revealed swelling and small areas of perforating ulcers of the gingival mucosa in the region of teeth 14 and 15, which presented tooth mobility (**Supplementary File 1-A**). The radiograph showed vertical alveolar bone loss along the roots (appearance of "floating teeth"), and reaching the apical third of teeth 14 and 15 (**Supplementary File 1-B**). A new biopsy confirmed the recurrence of LCH. The lesion was excised under local anesthesia, and the affected teeth were extracted.

The patient remained asymptomatic for 3 years, when she complained of persistent headache lasting for more than a month, for which reason she was referred to neurology for evaluation. A CT scan of the skull revealed an osteolytic lesion at the base of the skull in the occipital region (**Supplementary File 2**). Surgical excision was performed by the neurosurgery team at Hospital da Baleia in Belo Horizonte, and histopathological analysis confirmed LCH. The patient also underwent chemotherapy treatment weekly for a year. A bone scintigraphy showed no other active lesions. The patient was monitored jointly by the oncology team and the stomatology and oral and maxillofacial surgery service.

After five years, the patient reported high mobility of tooth 26. Clinical evaluation revealed poor healing and ulceration in the left posterior maxilla. Incisional biopsy confirmed another recurrence of LCH. Surgical excision was performed. Due to significant bone and soft tissue loss, an oroantral communication was generated (**figure 5-A**)



and repaired with a mucoperiosteal flap and buccal fat pad (**figure 5-B**). Postoperative healing was satisfactory (**figure 5-C**).

Six months later, the patient returned with new signs of recurrence in the posterior right mandible, with ulceration and mobility of teeth 44, 45, and 47 (**figure 5-D**). A new incisional biopsy was then performed, which confirmed the diagnosis of LCH. Total excision of the lesion and an extraction of involved teeth were performed.

In March 2022, three months after the last surgical intervention, a follow-up imaging CT revealed a lesion causing erosion of the left frontal bone, associated with laminar dural thickening, multiple cystic pulmonary lesions and osteolytic formations in the right iliac bone and in areas of the T12 vertebral body. A diagnosis of multisystemic LCH recurrence was made, and chemotherapy was resumed. The chemotherapy regimen was completed in January 2023

Table 1

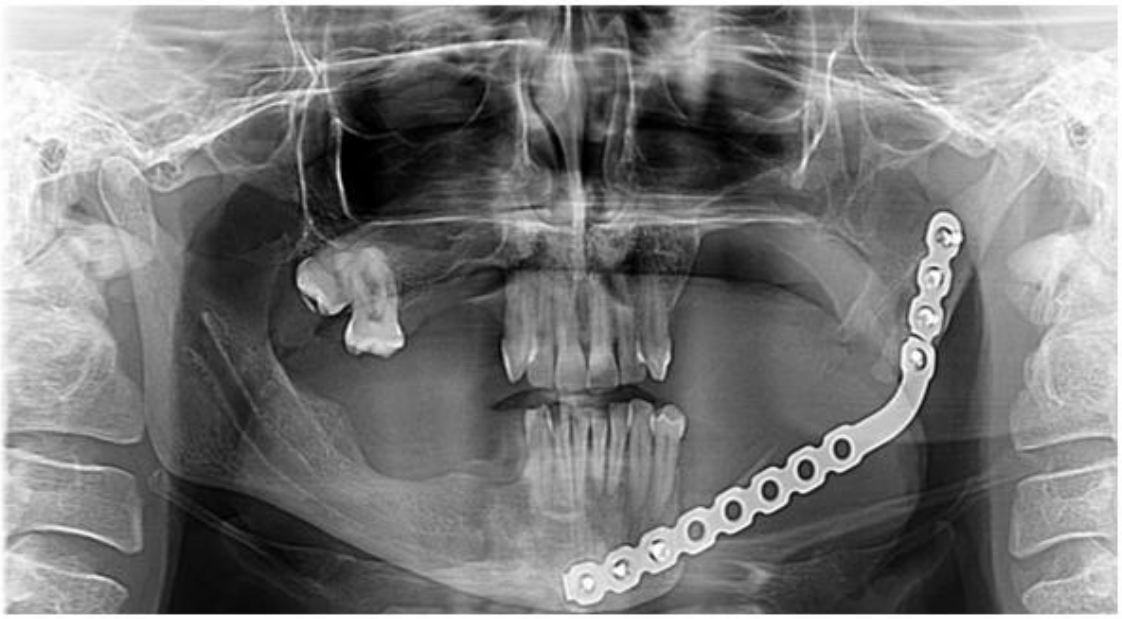
Table 1: Oral and systemic manifestations and proposed intervention.

Manifestation/year	Clinical and/or imaging findings	Intervention
1st manifestation / April 2012	Ulceration and increased volume in the gum inserted in the region of teeth 37 and 38, with mobility.	Excision of the lesion with removal of the involved teeth followed by referral for laboratory tests, which showed no changes.
2nd manifestation / January 2013	The panoramic radiograph showed an increase in the radiolucent area in the previously operated region, with a multilocular appearance, and extending from the postoperative region to the base of the mandible.	Two sessions of intralesional infiltration of 5 ml of methylprednisolone sodium succinate (62.5 mg/ml, totaling 312.5 mg), with a 15-day interval between them. After a mandible fracture, segmental resection of the mandible and bone fixation with reconstruction plates and screws were performed.
3rd manifestation / October 2013	Perforating ulcers of the gingival mucosa in the region of teeth 14 and 15, which presented dental mobility.	Excision of the lesion and removal of teeth 14 and 15.
4th manifestation / August 2016 (extra-oral manifestation)	Complaint of persistent headache and head CT revealed an osteolytic lesion at the base of the skull in the occipital region.	Excision of the lesion followed by chemotherapy.
5th manifestation / September 2021	Ulcerations on the gingival margin, generalized bone loss and tooth mobility of elements 25 and 27.	Excision of the lesion and removal of elements 25 and 27, in addition to tissue transposition of a mucoperiosteal flap and use of the cheek adipose body for bone coverage.
6th manifestation / December 2021	Ulceration in the posterior region of the right jaw, in	Excision of the lesion and removal of elements 44, 45 and 47.

	addition to mobility and gingival recession in elements 44, 45 and 47.	
7th manifestation / March 2022 (extra-oral manifestation)	CT showed a lesion causing erosion of the left frontal bone, associated with laminar dural thickening, multiple cystic pulmonary lesions and osteolytic formations in the right iliac bone, and also in areas in the T12 vertebral body.	Chemotherapy.

CT, computed tomography.

shows the main clinical and imaging manifestations and the proposed treatment over the years. The patient is currently being monitored by the oncology and oral and maxillofacial clinic with periodic consultations, without signs of recurrence of the lesion in the oral and maxillofacial region (**figure 6**).



Discussion

In the present study, we report a case of an unusual presentation of LCH, with systemic involvement and multiple recurrences in a female patient diagnosed in the third decade of life. LCH is a rare disease, with an incidence ranging from 5 to 9 cases per million in children[14,15], and 1 case per million in adult patients[16] , with a slight predilection for males[14]. Other authors have similarly reported LCH in adults[9, 17,18].

Oral manifestations of LCH include involvement of bone tissue and oral mucosa. Clinical signs such as gingival ulceration, gingival recession, erythema, bone destruction, and tooth mobility and loss may be present[8], sometimes leading to the misdiagnosis of periodontal disease. In the case in question, the first therapeutic approach performed was unsuccessful endodontic treatment. In this context, dentists play a fundamental role in the diagnosis and treatment of LCH, since in 77% of cases the oral manifestation of the disease occurs and in many cases it is the only site of manifestation[8,19].

After diagnosis, it is essential to maintain periodic follow-up of individuals with LCH, due to its challenging clinical course[8]. In the case of this patient, after the first manifestation, she presented recurrence in less than a year after the surgical intervention, with new oral and systemic alterations. In addition to oral involvement, the lesion affected the lung and bone tissue, characterizing it as multisystemic and multifocal, involving bones of the skull, hip and jaw. These findings highlight the importance of a multidisciplinary approach in the follow-up of these patients.

The treatment of LCH varies according to the extent and location of the lesions and may involve from local surgical intervention to systemic therapies such as chemotherapy and radiotherapy[8,10]. Defining the therapeutic strategy is essential to reduce complications, prevent recurrences, and improve the quality of life of these individuals,

especially in cases with multifocal involvement[10]. In the case reported, the initial approach consisted of surgical excision of the primary lesion in the region of teeth 37 and 38. Despite periodic monitoring, the patient presented recurrence six months after the first intervention, with expansion of the lesion in the mandible. Initial conservative treatment with corticosteroid injections was not effective, leading to the need for segmental bone resection and reconstruction with a titanium plate, due to a pathological fracture.

Recurrence is a major challenge in LCH, with variable frequency depending on the type of involvement and response to initial treatment. Studies suggest that cases involving only one site have a more favorable prognosis, while systemic cases have a higher risk of recurrence[11,13]. In the case presented, the disease evolved with new oral and systemic manifestations, including involvement of the cranial skeleton, maxillary region, lungs, iliac bone and vertebral body.

The BRAFV600E mutation has been found in more than 50% of LCH cases[20]. This discovery was fundamental in understanding the pathogenesis of the disease as a myeloid neoplasm and not simply as a reactive or inflammatory condition[20]. These findings were also significant in advancing the understanding of the clinical behavior and prognosis of LCH, since the BRAFV600E mutation has been associated with more aggressive forms of the disease and higher recurrence rates[21]. Understanding these mutations in diseases with challenging clinical courses such as HCL has been important for the development of targeted therapies with better results.

A multidisciplinary approach involving stomatology, oncology and oral maxillofacial surgery is crucial in the management of LCH, especially in cases of recurrence or systemic dissemination. Early detection of lesions, periodic monitoring and individualization of treatment are essential to optimize the prognosis and quality of life of patients affected by this condition.

Conclusion

LCH is a rare disease with challenging management, which can present a variable clinical course and local and systemic manifestations, being the oral cavity frequently affected. Recurrence of the disease, even after surgical interventions and treatment with corticosteroids, highlights the need for rigorous monitoring and therapeutic strategies with a multidisciplinary team, especially in cases with systemic involvement.

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AUTHORS' CONTRIBUTIONS

N.C.M.S. and J.A.S. contributed to the writing. H.C.L. and R.C.L. were responsible for the revision and translation. S.A.A. and R.G.R. participated in the diagnostic approach and treatment of the reported case and revised the text. J.C.T.L. supervised the manuscript, participated in the diagnostic approach and treatment of the reported case, and revised the text. All authors reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Competing interests: The authors have no conflicts of interest to declare.

Ethics approval:

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Figure legends

Figure 1. A) Extraoral view demonstrating slight facial asymmetry on the left side of the lower third of the face. **B)** Radiographic image revealing a lesion associated with teeth 37 and 38.

Figure 2. Microscopic features of Langerhans cell histiocytosis described in the present report. **A)** The lesion consisted of cells presenting pale and grooved nucleus with abundant eosinophilic cytoplasm. Eosinophils were commonly observed (H&E; 100X). **B)** The lesion was positive for CD1a (DAB; 100X), **C)** for CD207 (DAB; 200X); and for **D)** S100 proteins (DAB; 100X).

Figure 3. A) Radiographic image obtained a few days postoperatively. **B)** Radiolucent area in the previously operated site, presenting a multilocular appearance and extending from the surgical region to the base of the mandible. **C)** Pathological fracture of the left mandibular body.

Figure 4. A) Three-dimensional prototype of the mandible on the left and mirrored prototype on the right, with a pre-shaped titanium reconstruction plate. **B)** Surgical marking for submandibular access. **C)** Intraoperative view of the lesion. **D)** Final fixation following segmental resection. **E)** Postoperative contralateral occlusion demonstrating stability in maximum intercuspation. **F)** Postoperative panoramic radiograph showing appropriate positioning of 2.4 system plates and screws, with no evidence of recurrence.

Figure 5. A) Intraoperative view showing resection of the affected mucogingival tissues and alveolar bone, resulting in an oroantral communication. **B)** Mobilization of the buccal fat pad and repositioning of the mucoperiosteal flap for closure of the communication. **C)** Postoperative view demonstrating satisfactory healing of the surgical site. **D)** Right

posterior mandible showing gingival recession and ulceration adjacent to teeth 44, 45, and 46.

Figure 6. Follow-up radiographic image showing appropriate fixation of the titanium plate and no evidence of recurrence.

Suplementary File 1. A) Clinical examination of the left maxilla showing ulceration and gingival recession involving teeth 14 and 15. **B)** Radiographic view of the left maxilla revealing radiolucent areas adjacent to teeth 14 and 15.

Suplementary File 2. Axial computed tomography (CT) scans of the skull showing hypodense areas with cortical erosion in the occipital bone.