J Oral Med Oral Surg 2022;28:46
https://doi.org/10.1051/mbcb/2022027

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JOMOS
Journal of Oral Medicine and Oral Surgery

Case Report

Diagnosis, treatment and recurrence of a mandibular Langerhans cell histiocytosis: a three-year follow-up case report

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(Received: 19 June 2022, accepted: 11 September 2022)

Keywords: histiocytosis / langerhans cells / mandible

Abstract – Introduction: Langerhans cell histiocytosis (LCH) is an abnormal clonal proliferation of Langerhans cells secondary to immune process, mutation of oncogene or genetic predispositions. It preferentially affects bone, lung and skin. The incidence is 2–6 cases per million per year. Prognosis is variable and depends on number and location of lesions, and impact of the initial treatment. Oral lesions may be the first sign of LCH as illustrated by the present case. **Observation:** A 24-year-old male consulted first for severe gingival inflammation, teeth mobilities and alveolar bone loss with a suspicion of LCH. A pulmonary involvement was secondarily revealed by tomodensitometry. Histological examination, from gingival biopsy, confirmed the diagnostic of LCH, showing cells positive for the anti-CD1A antibody. The patient was managed by oral surgery and chemotherapy approaches. Alveolar bone loss significantly reduced. But 2 years and a half after the diagnosis, a recurrence was noted and managed by surgical approach. After a three-year follow-up, no recurrence was noted. **Conclusion:** Oral lesions can be inaugural manifestations of LCH. The dentist has an essential role in the early detection of these lesions.

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease with an incidence of 2–6 cases per million per year [1,2]. LCH is defined as a proliferation of cells with similar phenotype as Langerhans cells. Langerhans cells are macrophagic cells normally present in squamous and pulmonary epithelia [3]. The pathogenesis of the LCH remains debatable [4].

LCH may develop in various tissues such as bone, lung, liver, skin or endocrine systems, lymph nodes, nervous and digestive systems [5]. Bone involvement is discernible in half of the LCH patients, mandibular in particular [2]. In these patients, LCH leads to osteolytic lesions revealed by pain, swelling and dental mobilities [6].

In the case reported, oral lesions were the first manifestation of LCH and a three-year follow-up was documented including a recurrence episode.

Observation

A 24-year-old man was referred to the Oral Surgery department for mandibular dental mobilities, mandibular pain and halitosis for a few weeks.

He had no personal and family medical history and did not take any medications. He smokes about 15 cigarettes per day for about 5 years.

The extraoral examination revealed a left submandibular swelling. A painful homolateral cervical lymphadenopathy was noticed. No hypoesthesia of the inferior alveolar nerve was noted. The intraoral examination showed a severe gingival inflammation and a large amount of dental plaque on all teeth. The interdental mandibular papillae were ulcerated. The lower incisors and left molars were mobile. All mandibular

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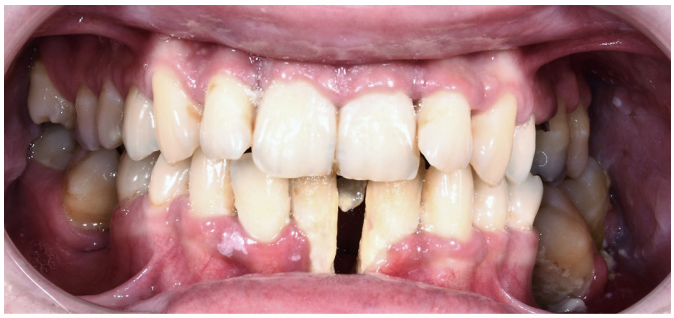
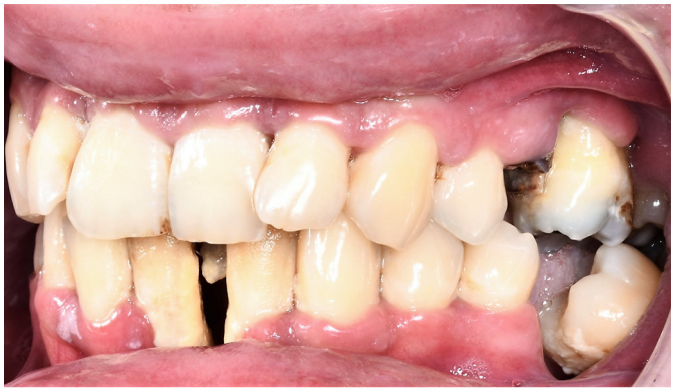


(a)



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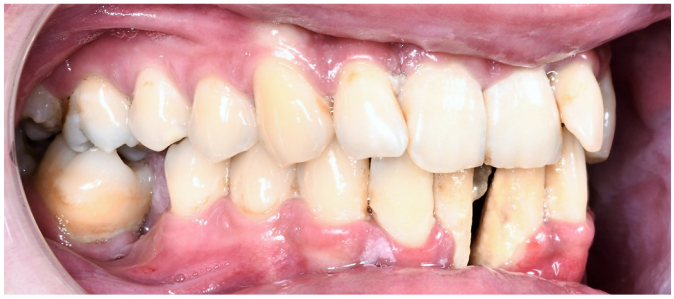

(c)

Fig. 1. Gingival inflammation and ulceration of papilla, predominantly in anterior mandibular area. (a) Frontal view, (b) left lateral view, (c) right lateral view.

teeth were vital except for the left inferior central incisor (Figs. 1a–1c).

The panoramic radiograph revealed a multilobular radiolucent image in the periapical area of the mandibular incisors and a severe alveolar bone loss around the left mandibular molars giving an impression of "floating teeth" (Fig. 2).

Periodontal disease, *i.e.* periodontis, was the first hypothesis for diagnosis. But severe alveolar bone loss combined with molar mobilities with a such impression of "floating teeth" may raise suspicion of a systemic pathology. Once again, the patient reported no history of family history of periodontal disorder. Therefore, gingival and bone biopsies in mandibular incisors area as well as blood tests and serologies were performed. Blood tests revealed a hyperleukocytosis (10.85 G/L), hypophosphatemia (0.73 mmol/L) and slight hypercalcemia (2.66 mmol/L). HIV, HBV, HCV status were negative.

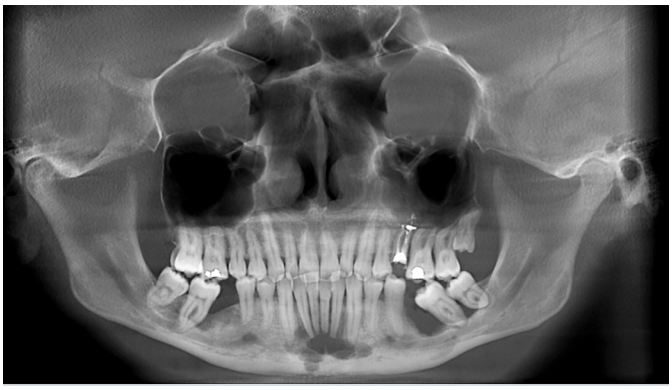

Fig. 2. Panoramic radiograph showing important alveolar bone loss, in particular around left mandibular molars, and multilobular radiolucent image in the periapical area of the mandibular incisors.

Histological examination confirmed the diagnosis of LCH. Cells with eosinophil cytoplasm and reniform nuclei were detected in gingival and bone biopsies (Fig. 3a). Immunohistochemical staining was highly positive for the anti-CD1A antibody (Fig. 3b) and negative for the anti-CD68 and anti-PAB cytokeratin antibodies in gingival and bone biopsies.

The patient was referred to the department of internal medicine for further investigations. Abdominal and pelvic ultrasonography did not find any hepatosplenomegaly or lymphadenopathy. The tomodensitometry confirmed mandibular osteolysis and revealed bilateral pulmonary microcysts.

One month after the diagnosis, a chemotherapy was started. During the 6-week induction phase, the patient received 10 mg intravenous vinblastine per week, 60 mg corticosteroids per day during 4 weeks, reduced to 40 mg per day during 1 week and 20 mg per day during the ultimate week.

The maintenance phase lasted for 30 weeks. The patient received every 3 weeks a treatment of 10 mg intravenous vinblastine the first day, 60 mg corticosteroids for the first five days and sulfamethoxazole (400 mg) and trimethoprime (80 mg) every day to prevent pneumocystosis.

The patient was encouraged to improve his oral hygiene and quit smoking to limit the risk of periodontal disease which could worsen bone loss initially caused by LCH. The chemotherapy was well tolerated with no neurological side effects detected. After 9 months of such treatment, peripheral new bone formation in mandibular lesions, reduction of dental mobility and regression of pulmonary cysts were observed (Fig. 4).

One year after the diagnosis, curettage of symphyseal lesion and extraction of five mobile teeth (25, 32, 37, 41 and 42) were performed. Tooth 31 was already avulsed spontaneously. Clinical and radiological follow-up during 1 year did not find any recurrence and showed stability of pulmonary microcysts. Smoking cessation wasn't achieved and oral hygiene was still insufficient despite the repeating encouragements.

Two years and a half after the diagnosis, a routine cone beam computed tomography (CBCT) showed a recurrence in the right parasymphyseal mandibular area (Fig. 5). A new surgical

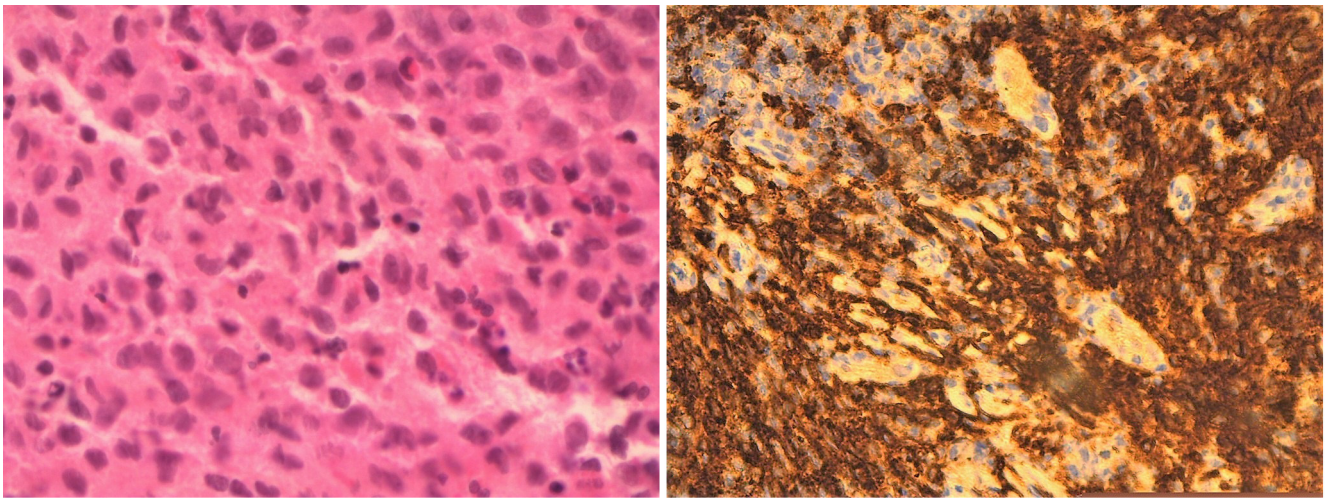

Fig. 3. Gingival and bone biopsies examination show Langerhans cells with eosinophil cytoplasm and reniform nuclei. (a) HES stain, original ×200, (b) anti-CD1a IHC, original ×200.

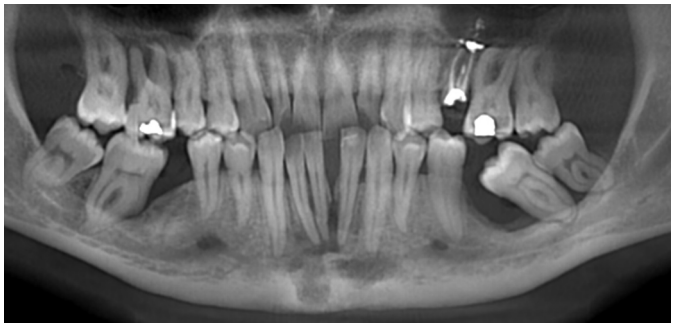

Fig. 4. Ten-month follow-up, panoramic radiograph showing reduction of bone loss after chemotherapy (compare to Fig. 2).

curettage was performed. After 6 months, no clinical and radiological recurrence was observed (Fig. 6) and pulmonary microcysts were constant. A follow-up every 6 months was established to detect clinical (pain, tooth mobility, gingival inflammation) and radiological (osteolysis) signs of recurrence.

Discussion

LCH is a disease characterized by an abnormal clonal proliferation of cells with similar phenotype as Langerhans cells as identified in this case. These cells are dendritic cells usually found in squamous and pulmonary epithelia [1,3,4].

Histologically, LCH is characterized by a cellular infiltration of Langerhans cells organized in granuloma with Birbeck granules in the cytoplasm. These cells express the CD1A, as in the present case and/or CD207 (langerin) antigens and the S-100 protein [1,2,6,7].

Bone and skin lesions are the most common [2,8]. Any bone site can be affected with a predisposition for the skull, spine, ribs, pelvis, femur and mandible. Lung, liver, skin, endocrine system, lymph node, central nervous system and digestive system can also be affected. Pulmonary lesions are found in 90% of the active smokers affected by LCH like in the present case [2,5,8,9].

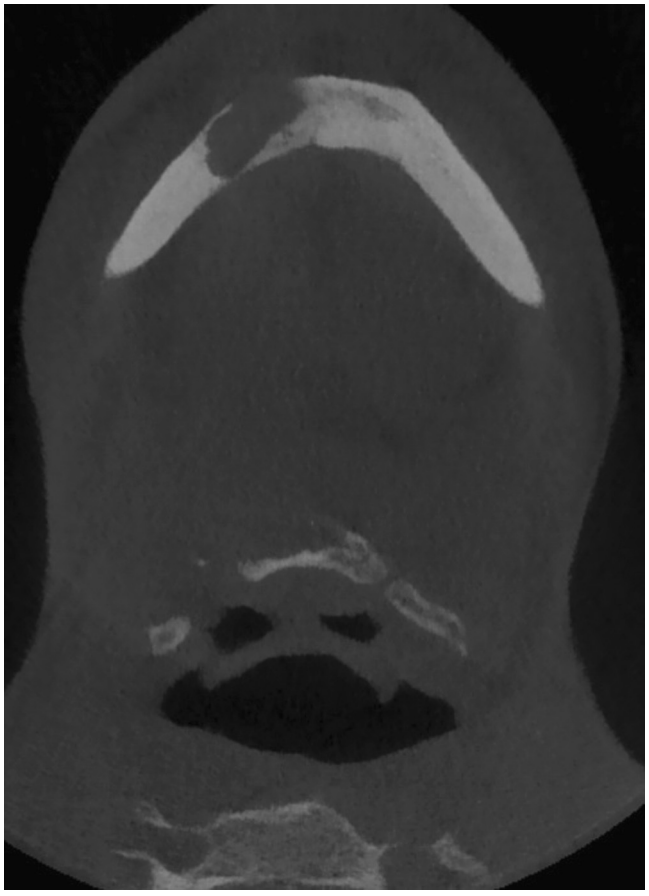

Fig. 5. Cone Beam Computed Tomography showing a recurrence on the mandibular symphysis 2 years and a half after the initial diagnosis.

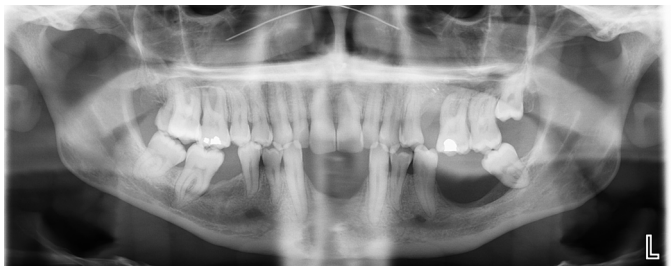

Fig. 6. Panoramic radiograph showing new bone formation of mandibular lesions 3 years after the initial diagnosis.

The pathogenesis of LCH is poorly deciphered. Different causes of cell proliferation have been found such as reaction to an immune process, mutation of the BRAF-V600E oncogene and genetic predispositions [1]. The mutation V600E in BRAF oncogene is find in 38–60% of LCH lesions [9]. This mutation activates the RAS-RAF-MEK-ERK-MAP kinase pathway responsible of proliferation, differentiation, migration and cells survival. Cells originate from the bone marrow accumulate into tissues and release metalloproteases which destroy these tissues [2].

The natural history of LCH is periods of remission and recurrence. For unifocal lesions, a spontaneous remission can be observed [2,3].

Oral lesions may be the first sign of LCH [6]. They are found in 7.4% to 77% of cases [1,6,10,11]. Clinical signs mainly reported are pain, swelling, ulcerations, gingival bleeding, dental mobility, premature tooth loss and lack of mucosa healing after tooth extraction [1,4,10,12]. Differential diagnosis include periodontal diseases, periapical diseases, odontogenic cyst, oral cancers, lymphoma, myeloma or ameloblastoma [1,4,6,7]. In the present case, oral manifestations as tooth mobilities and gingival inflammation were the first sign of the LCH.

Of oral manifestations, 67% affect bone tissue, the posterior mandible in particular [1,4,7,12,13]. They can be isolated or multiple and moderate to severe. On X-rays, periodontal bone loss shows an impression of “floating teeth”. Soft tissue lesions can be gingival ulcerations or enlargements [1,7,11] as in the present case.

Complete healing is obtained in almost all cases after treatment. There is no reference treatment for LCH [14]. Different therapeutic options, oftenly combined, are available. It may combine surgical management with radiotherapy, targeted therapy or chemotherapy using cytotoxic agents (vinblastine, etoposide) and intralesional injection of α-interferon or corticosteroids [5,7,8,10,14,15]. A such multimodal approach was performed in the present case. If LCH is resistant to therapeutics mentioned above, has severe symptoms and/or multisystemic involvement, BRAF inhibitors may be used [16].

Surgical treatment only is recommended for patients with lesions limited to the oral cavity [12,13]. Systemic treatments must be combined if any other organ is affected like in this case where pulmonary microcysts where identified.

Most of the time, prognostic is very good with 5-year survival ranging 75% to 100% [7] but recurrences can appear after successful initial treatment [12]. Oral recurrences may occur in separate locations than the first episode of LCH but with the same aspect. Risk factors for recurrences are the young age of the patient and presence of systemic lesions [1]. In the present case, the recurrence occurs in the mandibular symphysis.

Conclusion

Dentists, oral surgeons and maxillofacial surgeons have a crucial role in the diagnosis of LCH as oral manifestations are frequent, often isolated and sometimes inaugural. They also play a part in the multidisciplinary management and follow-up to encourage oral hygiene, to perform appropriate dental care and to promote smoking cessation.

Conflicts of interest

The author declares that she has no conflicts of interest in relation to this article.

Informed consent

The author declares that informed consent not required.

Ethical committee approval

The author declares that Ethical approval not required.

Source of funding

This research did not receive any specific funding.

Acknowledgments. The authors acknowledge Drs Elisabeth Cassagnau, Juliette Eugène-Lamer, Anne Moreau and Eric Lagrue, Nantes University Hospital, for histologic examinations and for histological images.

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