Hand–Schüler–Christian disease presenting with recurrent, bilateral, symmetrical mandibular lesions in an 8-year-old boy: report of a case

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Introduction
Langerhans cell histiocytosis (LCH) is a group of diseases characterized by clonal proliferation of cells with features of Langerhans cells (LCs).1,2 It is classified according to the spread of the disease into the unisystem LCH that includes unifocal and multifocal forms, and the multisystem LCH.3–5 The unisystem unifocal form corresponds to the eosinophilic granuloma, the unisystem multifocal one to the Hand–Schüler–Christian disease (HSC), and the multisystem one to Abt–Letterer–Siwe disease.

LCH is a disease of childhood as it is most frequent to 1- to 3-year-old children.6,7 An isolated bone lesion is usually seen in 5- to 15-year-old children, HSC disease is primarily seen in infants and children and rarely affects adults, while the multisystem disease begins before the age of 2, but it may also manifest in newborns.8,9 In a case series including 29 children (<15-years old) with LCH, 69% had single system and 31% multisystem disease, with approximately 45% of those with unisystem LCH presenting the unifocal form and 38% the multifocal one.10 Overall, the incidence of LCH is estimated at 0.4 new cases in 100,000 children up to 15-years old, with the male to female ratio ranging from 1.1:1 to 4:1.8,11

The unisystem form usually affects the bones, with the skull, ribs, pelvis, scapula, and mandible being the most common locations.12,23 In the skull, the calvaria is affected more often than the base, especially in the parietal region. From the long bones, the femur is the most commonly affected, followed by the humerus and the tibia.14,15 Bone involvement may be asymptomatic or accompanied by swelling and pain of the affected area, pathologic fracture or optic atrophy and otitis media as a result of adjacent bone involvement.8 Systemic and central nervous system involvement, delay in sexual maturity and bone development may result due to the involvement of the pituitary gland and hypothalamus.16,17 Approximately 1/3 of...
the patients with HSC disease present with the classical triad of exophthalmos, calvarial lytic lesions, and diabetes insipidus due to extension from the calvarial bone to the posterior pituitary stalk of the hypothalamus. \(^{18,19}\) Diabetes insipidus may be the first manifestation of HSC disease.\(^{20-23}\)

Head and neck lesions are found in 70% to 90% of patients with LCH, mostly in the temporal bones, jaws, and skin of the auditory meatus and they may be the earliest or the only sign of the disease.\(^{24}\) Recognition of early, non-specific signs could facilitate early diagnosis of the disease.\(^{25,26}\) In a study of 314 patients, aged 2 months to 83 years, osseous lesions were present in 60%, of whom 6.7% had mandibular lesions,\(^{27}\) while in a review of 1.120 cases of LCH yielded 73% of 114 cases with oral involvement had mandibular lesions. The mandible is more frequently involved than the maxilla,\(^{28}\) usually the posterior portion of the body and the angle.\(^{28}\)

Microscopic examination in all forms of LCH shows infiltration by Langerhans cells and eosinophils, as well as macrophages, lymphocytes, plasmacytes, and giant cells.\(^{29,30}\) Positive immunohistochemical reaction for CD1a antigen and S100 protein, as well as ultrastructural presence of Birbeck’s granules, is diagnostic of LCH.\(^{31,32}\)

We present the case of an 8-year-old boy diagnosed with HSC disease that manifested bilateral symmetrical lesions in the posterior mandible, recurring 2 years after chemotherapy.

**Case report**

An 8-year-old boy was referred for diagnosis and management of acute pain of the mandibular area, of 1 week duration. He had been diagnosed with HSC disease at the age of 11 months, due to multiple osteolytic lesions and diabetes insipidus. Osteolytic lesions were initially identified in the right supramastoidal and the right lithoid bone, both accompanied by soft tissue swelling, and the right temporal and temporoparietal region; decreased bone density was seen in the left tibia, while right subarachnoid hemorrhage was, also, present. Systemic chemotherapy (vinblastine, 3 mg/m\(^2\) IV, every 3 weeks and prednisone, 20 mg/m\(^2\), orally 5 days with vinblastine) was administered for 1 year, along with desmopressin (0.025 mg/m\(^2\) day, 0.05 mg/m\(^2\) night, nasal spray, daily) for the management of diabetes insipidus.
Two years later, at the age of 3 years, the patient presented with osteolytic lesions in the upper metaphysis of the left humerus and in the occipital bone, hypothyroidism, growth hormone deficiency and polyuria. He was treated with further systemic chemotherapy (vinblastine, 4.7 mg/m² IV, every 3 weeks; prednisone, 30 mg/m², orally ×5 days with vinblastine, mercaptopurine, 12.5 mg/m²; methotrexate, 7.5 mg/m²) for 1 year. He is also being treated for hypothyroidism (tetraiodothyronine, T4: 50 μg, orally, for 4 days/week and 75 μg, orally, the next 3 days of the week), diabetes insipidus (minirin, 60 μg, sublingually, 3 times/day) and growth hormone deficiency (hydrocortisone, 12.5 mg/day, in 3 doses, orally, during meantime, without the administration of prednisone).

Extraoral examination revealed swelling of the right mandible, but no exophthalmos was noted (Figure 1A). Intraoral examination showed bilateral, pressure-sensitive swellings of the buccal and lingual areas of the lower second primary molars. The teeth showed mobility on percussion and the remaining gingival tissue showed only mild inflammation (Figures 1B to F).

In the panoramic radiograph, well-defined, extensive osteolytic lesions around the primary molars were observed, with involvement of the apices, without any significant dental pathology (Figure 1G). Treatment consisted of extractions of lower second primary molars under local anesthesia (articaine hydrochloride 4% with adrenaline 1:100,000) (Figures 2A and B).

Due to the previous diagnosis of LCH part of the surrounding the molars soft tissues were excised, fixed in 4% buffered formalin and submitted for pathologic examination. Hematoxylin–eosin stained sections showed a dense infiltration by large epithelioid cells with indented vesicular nuclei and ample eosinophilic cytoplasm, admixed with eosinophils. Immunohistochemistry revealed positive epithelioid cells for CD1a (B) and S100 protein (C).

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The boy was referred to the pediatric oncological clinic for further evaluation and management. He received an induction regimen according to the LCH-1 study protocol, with vinblastine (6 mg/m², IV, every three weeks) for 21 cycles of treatment for 1 year plus oral prednisone. Oral prednisone was started at a dose of 40 mg/m² per day, for 5 days simultaneously with the administration of vinblastine, followed by a long tapering period. At the same time, the patient presented again with growth hormone deficiency, and treated with somatropin human recombinant (4 mg, SC, 6 days/week). Several drug doses were adjusted during treatment, depending on his medical examinations and his reaction to chemotherapy treatment, each time. During the chemotherapy period, oral examinations were performed at 1-, 2-, 4-, 8-, and 12-month intervals. The symptoms improved and the lesions decreased in size considerably in the 1-year follow-up (Figure 4).

Patient was not seen for 1 year, after the last visit, since his place of residence was on a remote Greek island. Two years after the diagnosis of LCH due to the mandibular lesions, at the age of 10 years, he presented again with new lesions in the area of the mandibular first permanent molars (Figures 5A to C). A new biopsy was performed from both sites, confirming recurrent LCH. A new cycle of chemotherapy was initiated but with a modified protocol, as the time of recurrence of the mandibular lesions was just 2 years. This protocol included vincristine, cytarabine and prednisone (1st day: vincristine, 2 ml, IV, and cytarabine, 134 ml, SC and 2nd, 3rd, and 4th day: cytarabine 134 ml, SC, every three weeks for 6 cycles of treatment, plus oral prednisone [11 pills of 5 mg/m² each per day]) for 5 days simultaneously with the 1st day administration of the chemotherapeutic drugs. The 6-month follow-up revealed improvement of the clinical and radiographic appearance of the mandibular lesions (Figures 6A to D) and after one year panoramic x ray (Figure 7). The chemotherapeutic protocol will continue for 2 years, with drugs depending on the findings, in order to prevent a new recurrence.

Discussion
In the case presented herein, a boy with HSC disease, featuring multiple osteolytic lesions and diabetes insipidus presented with acute pain, mobility of the mandibular molars and gingival swelling. Pain, tooth mobility, and swelling are the most common presenting symptoms. Prolonged pain and tooth mobility are the most common symptoms of HSC disease. The symptoms vary among patients, with many having pain, tooth mobility, and swelling of the jaws. In some cases, the disease can lead to life-threatening complications. The presentation of pain and tooth mobility is consistent with the clinical findings observed in this case.
signs and symptoms of LCH, followed by headache, sensory disturbances, facial asymmetry and limited mouth opening. In the study of Ardekian et al., eosinophilic granuloma of the jaws initially manifested with pain in 44% of the patients and swelling in 48%. Deep periodontal pockets due to the destruction of the alveolar bone may also be seen and this is followed by intense tooth mobility. As those signs and symptoms are nonspecific, diagnosis may be postponed, in particular when those are the earliest or the only sign of the disease. LCH is common in the posterior region of the mandible, while bilateral involvement is not uncommon.

A mandatory step toward obtaining diagnosis of the disease in the oral cavity is the accurate clinical and radiographic differentiation diagnosis. It is necessary to consider a number of both benign and malignant bone lesions (unifocal entities in children: odontogenic cyst, periapical lesions, metastatic neuroblastoma, infarabonyhaemangioma, fibrous dysplasia, epidermoid cyst, giant cell granuloma, haemophiliapsudotumor) as well as disorders of the oral cavity mucosa and periodontal tissues (parodontitis, submucous abscess, subperiostal abscess, trauma, necrotizing sialometaplasia, tuberculosis, deep mycotic infection, melanoma, Papillon-Lefèvre syndrome, cyclic neutropenia, hypofosfatasia). Radiographically, LCH shows bone destruction, usually with well-defined margins, causing the “teeth floating in the air” appearance. In one study only, LCH presented with tooth displacement in one out of two of the patients and root resorption in one of the six. In the present case, the patient was diagnosed with HSC disease approximately 6 years before presentation; therefore the association of oral manifestations with the disease was highly likely, while the panoramic radiograph was consistent with the “teeth floating in air” appearance.

Treatment based on chemotherapy, radiotherapy and systemic corticosteroids usually reduces morbidity and mortality. Patients with minimal involvement require minimal treatment, while treatment with systemic cytotoxic agents is based upon whether high-risk (liver, spleen, and bone marrow) or low-risk organs (skin, bone, lung, lymph nodes, gastrointestinal tract, pituitary gland, and central nervous system) are involved. Substitutive hormonal treatment is, also, required when there is damage to the pituitary/hypothalamus axis or there is a risk for progression to other endocrine problems or neuronal degeneration. However, specific treatment protocols for preventing or delaying hormonal impairment have not yet been determined. In our patient systemic vinblastine and prednisone administration reduced considerably the size of the mandibular lesions.

Prognosis of LCH depends mainly on the extent of the systemic involvement and the initial patient’s response to treatment. A grave prognosis is associated with wide dissemination of the disease, resulting in extraskeletal involvement. Although the patient’s age is a less important prognostic factor, when the age at first presentation is less than 2 years, mortality rises to 50%. Recurrence in HSC ranges from 1.6% to 25%, while the rate of recurrence in the mandible is 60%. In the present case, the initial response to treatment was satisfactory, but the disease recurred three times, 2, 5, and 7 years after initial diagnosis, the last two with mandibular lesions.

Conclusions
LCH disease is primarily seen in infants and children and mandibular involvement may be the earliest or the only sign of the disease. Its clinical appearance may resemble dental or periodontal pathology. As a consequence, dentists can contribute to a timely and valid identification of HSC disease, by differentially diagnosing, correctly, lesions of head and neck.

References