American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e928307
DOI: 10.12659/AJCR.928307

Received: 2020.09.02
Accepted: 2020.10.02
Available online: 2020.10.13
Published: 2020.11.24

Incidental Diagnosis on Orthopantomography of Langerhans Cell Histiocytosis with Multifocal Jaw Involvement: A Case Report of Single-System Disease

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 42-year-old
Final Diagnosis: Langerhans cell histiocytosis
Symptoms: Asymptomatic
Medication: —
Clinical Procedure: Biopsy • curettage
Specialty: Oncology • Pathology

Objective: Unusual clinical course

Background: Langerhans cell histiocytosis (LCH) is a relatively rare neoplasm with a strong inflammatory component. It has diverse clinical manifestations, which range from a single lesion or multiple bony lesions to severe multisystem involvement. Approximately 10% to 20% of cases of LCH occur in the jaw, with the posterior mandible being the site most frequently involved.

Case Report: We report on the case of a 42-year-old man who presented with bilateral osteolytic lesions in the posterior mandible that were incidentally discovered during routine radiographic screening. Histological examination of the specimen confirmed the diagnosis of LCH.

Conclusions: This case illustrates the importance of orthopantomography (OPG) as a screening tool in new patients to perform an overall evaluation of the teeth and surrounding structures, such as the bone, temporomandibular joint, and sinuses. Moreover, OPG can be used to screen for the presence of asymptomatic lesions that are often diagnosed incidentally on radiographs.

MeSH Keywords: Diagnosis, Oral • Histiocytosis • Jaw Diseases • Langerhans Cells • Osteolysis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/928307

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Background

Langerhans cells (LCs) are inflammatory dendritic cells that are derived from the bone marrow, migrate through the bloodstream to the epidermis of the skin and the epithelium of oral mucosa, and play an important role in development of local immune response [1]. These cells belong to the antigen-presenting cell family, which processes and presents foreign bodies (antigens) to T-cell lymphocytes and initiates adaptive immune response [1].

In the oral cavity, improper function or abnormal proliferation of LCs is associated with the initiation or development of various oral diseases, such as periodontitis, candidiasis, lichen planus, squamous cell carcinoma, and Langerhans cell histiocytosis (LCH) [2].

LCH is characterized by abnormal proliferation of LCs. Clinically, its presentation can range from affecting only a single system such as the skin or bone to a life-threatening multisystem disease that involves other organs, including the lungs, spleen, bone marrow, and liver [3]. The incidence of LCH in adults ranges from 1 to 2 cases per million, with a male predilection and a mean age at diagnosis of 35 years [4].

There is much debate about whether LCH represents a reactive process or a neoplasm. The monoclonal proliferation of LCs in addition to the somatic mutations in mitogen-activated protein kinase genes, such as *BRAF* V600E and *MAP2K1*, support an underlying neoplastic process [5,6].

LCH in the oral cavity may be the first presenting sign before the disease becomes apparent elsewhere in the body [7]. The posterior mandible is the site most commonly affected [8]. Advanced jaw lesions may perforate the bone and present as either ulcerative lesions or as gingival masses [9].

Radiographically, LCH presents as non-corticated, well-defined radiolucent areas around the teeth, resulting in a "floating-in-air" appearance. Histopathological examination is essential to confirm the diagnosis [8].

Treatment depends on the extent of the lesions. Accessible jaw lesions are conventionally treated with curettage, whereas low-dose radiation can be considered for inaccessible lesions [9]. Intralesional steroid injection is also effective in some cases [10].

In this paper, we report on a case of oral LCH, emphasizing the radiographic and histopathological findings and differential diagnoses of the disease.

Case Report

History and clinical examination

A 42-year-old man presented with a chief complaint of missing teeth, which he wanted to restore. The patient's medical history was not significant, and he denied taking any medications. Extraoral findings were unremarkable. Intraoral examination revealed multiple missing teeth, multiple remaining roots, and generalized moderate gingival inflammation with grade III mobility of the mandibular posterior teeth bilaterally. The patient denied tooth sensitivity or pain.

Radiographic findings

An orthopantomogram (OPG) showed bilateral, well-demarcated radiolucent (geographic pattern) lesions eroding the mandibular bodies in the premolar/molar areas with complete loss of alveolar supporting bone around the mandibular posterior teeth. One lesion epicenter was at the mid-root level. Another radiolucent lesion was noted on the right maxilla distal to the canine. There was no clear evidence of root resorption or

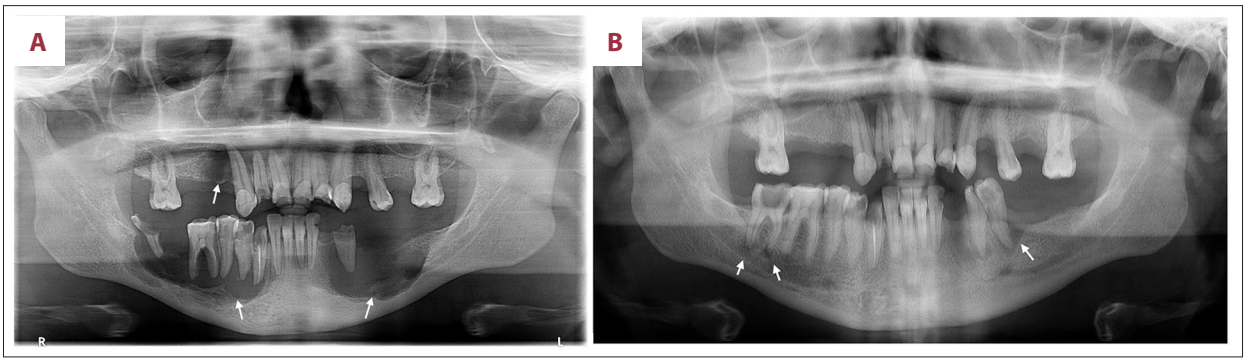

Figure 1. (**A**) An orthopantomogram (OPG) showing destructive radiolucent lesions on the mandible bilaterally and a third lesion distal to the right maxillary canine region. (**B**) An OPG taken 2 years earlier shows multiple small, periapical odontogenic lesions in the mandibular left premolars and the right molar.

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displacement or of septation of calcifications (Figure 1A). Only multiple small, periapical odontogenic lesions in the mandibular left premolars and right molar were observed, compared with an OPG taken 2 years earlier (Figure 1B).

A multi-detector computed tomography (CT) scan performed with bone window settings showed multiple non-expansible osteolytic (scooped-out shape) lesions associated with multiple floating teeth on the right anterior maxilla and bilaterally on the mandible. There was no evidence of calcification or septation (Figure 2A). The adjacent labial and buccal soft tissue and fat planes were preserved with no evidence of fat stranding or drainable collection. A CT scan performed after injection of iodine) showed no evidence of abnormal intralesional enhancement. There was no clear evidence of periosteal bone reaction. A whole-body (planar) CT scan and limited field of view, single-photon emission CT (SPECT-CT) scan were performed. The whole-body image showed increased uptake in both mandibular bodies, extending to the angle of the mandible (Figure 2B). There was no other uptake in the rest of the body. The SPECT-CT scan showed intense localized osseous uptake in the same areas in the right anterior maxilla and the mandible bilaterally, indicating a high level of metabolic activity (Figure 2C).

Differential diagnosis

Given the location of these lesions within the jaws (mid-root epicenter), punched-out radiolucent density, and the radiographic "floating- in-air" appearance of the teeth, LCH was considered the most likely diagnosis [8]. Other conditions were included n the differential diagnosis because of radiographic appearances.

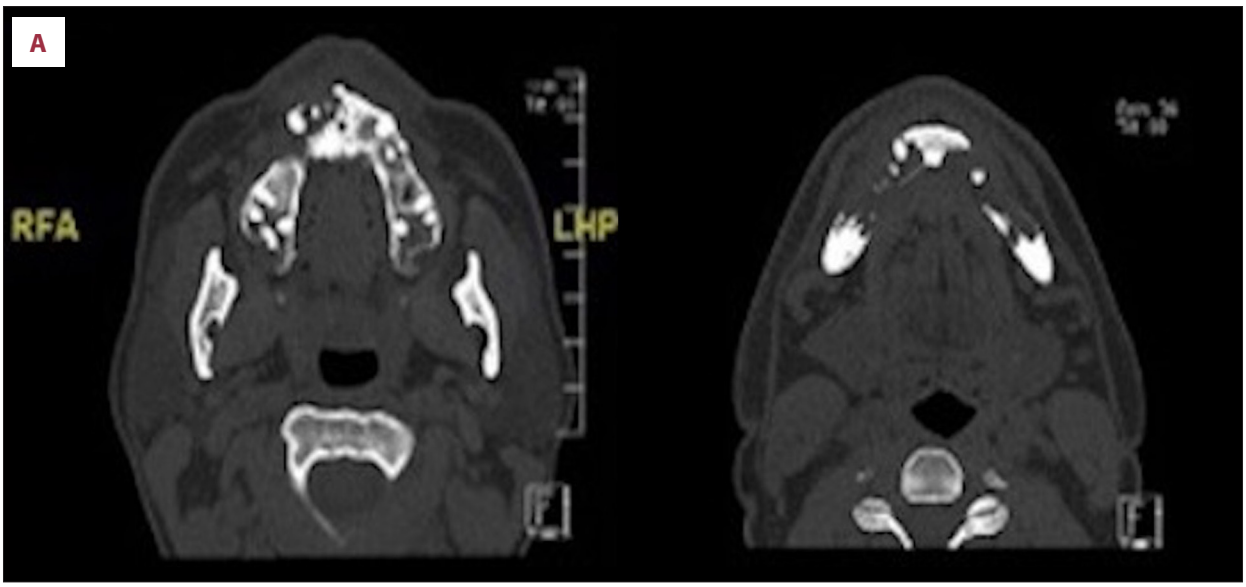
Primary intraosseous squamous cell carcinoma of the jaws was considered because of the rapid and aggressive bone destruction and the radiographic presentation of ill-defined radiolucent lesions [11]. The radiographic appearance of lytic radiolucent lesions with ill-defined margins raised the suspicion of malignancy [12]. Leukemia and lymphoma can present as multifocal intraosseous radiolucent lesions that tend to grow within the periodontal ligament spaces [13]. Ewing sarcoma can appear as aggressive intraosseous lesions with poor demarcated borders in posterior areas of both jaws [8]. Because calculus deposits were absent on radiography and the epicenters of the lesions were at the mid-root level, aggressive periodontal disease was considered the least likely diagnosis.

Laboratory investigations

A complete blood count was performed as well as testing for levels of triiodothyronine, thyroid stimulating hormone, free thyroxine, immunoglobulin (Ig) A, IgG, IgE, and alkaline phosphatase; erythrocyte sedimentation rate; minerals (sodium, potassium, and chloride); and renal and liver function. None of the results were significant for any underlying medical conditions.

Histopathological findings

Microscopic examination revealed a diffuse infiltrate of large cells with pale, eosinophilic cytoplasm intermixed with inflammatory cells that were predominantly composed of eosinophils. Immunohistochemical staining showed numerous large cells that exhibited immunoreactivity to CD1a, CD68, and S-100 antibodies (Figure 3).



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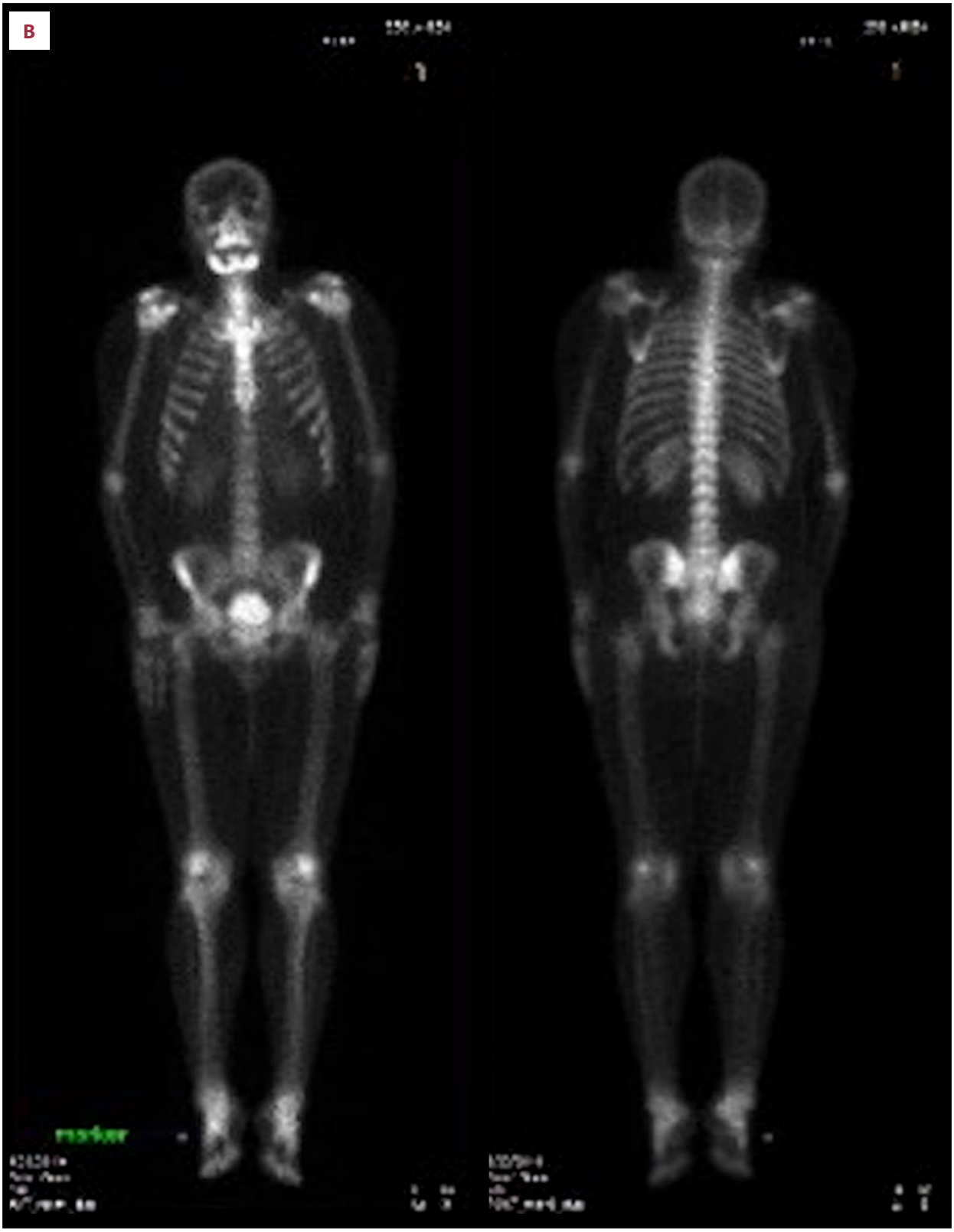

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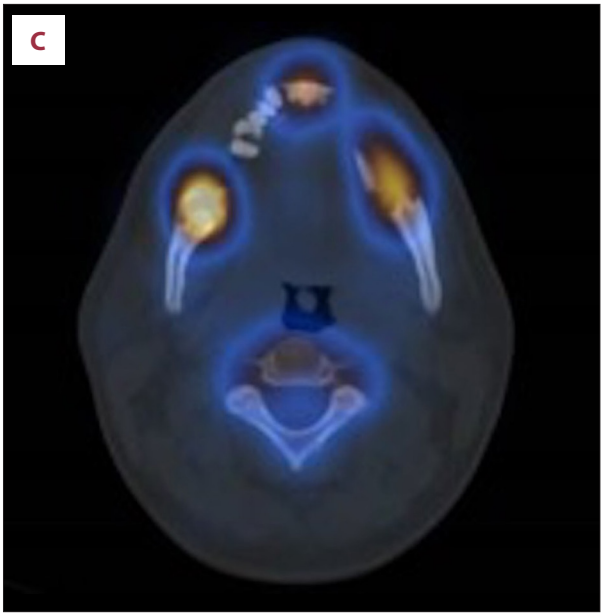

Figure 2. (**A**) Multi-detector computed tomography (CT) scans performed with bone window settings. The different axial-view slices of the maxilla and mandible show non-expansible osteolytic lesions in both the upper and lower jaws. (**B**) A whole-body bone CT scan showing increased uptake in the mandible. (**C**) A single-photon emission CT scan showing a high rate of metabolic activity in the same regions.

Diagnosis

The clinical, radiographic, and microscopic findings confirmed the diagnosis of single-system LCH with multifocal jaw involvement. The patient was referred to an oncology center to start appropriate treatment.

Discussion

LCH (previously known as histiocytosis X) can present in 3 different clinical forms, the most common (70%) and least aggressive of which is eosinophilic granuloma. Hand-Schüller-Christian disease is the chronic recurring form of multifocal LCH, with a triad that consists of diabetes insipidus, skull lesions, and exophthalmos. Letterer-Siwe disease, the most severe form of LCH, constitutes approximately 10% of cases and patients with it have multifocal, multisystem involvement [14].

Faber and Green observed that the different clinical forms of LCH had similar features on radiographic and histologic examination [15]. In 1953, Lichenstein and Jeffe grouped the different clinical forms under the term histiocytosis X, with the X denoting the uncertainty about the cell of origin [16]. The development of electron microscopy made it possible to identify intracytoplasmic rod- or tennis racquet-shaped organelles, called Birbeck granules. These were found specifically in normal epidermal LCs and were a pathognomonic feature of histiocytosis X lesions, thus establishing a histogenic relationship between the 2. Accordingly, histiocytosis X was renamed LCH [17].

In a retrospective study, the radiographic features of the disease in the jaws were reviewed in 29 patients diagnosed with histiocytosis X. The authors reported 7 characteristics that may be helpful in histiocytosis X identification: unifocal "intraosseous" lesions, multifocal "alveolar bone" lesions, the

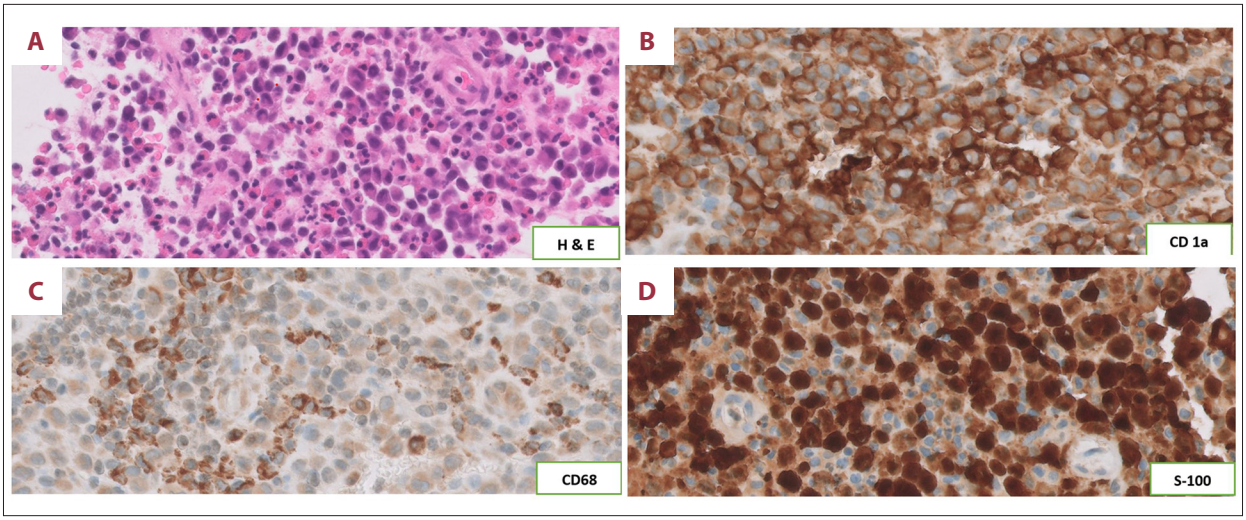

Figure 3. (**A**) A photomicrograph of a hematoxylin and eosin-stained section shows sheets of an infiltrate composed of large cells with abundant eosinophilic cytoplasm. In the background, variable numbers of inflammatory cells are present, primarily eosinophils (40×). Photomicrographs of sheets of large cells with immunohistochemical staining. (**B**) Immunoreactivity to CD1a antibody. (**C**) Immunoreactivity to CD68 antibody. (**D**) Immunoreactivity to S-100 antibody.

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"scooped-out" appearance in the alveolar process, well-defined radiolucency, prelesional sclerosis in the alveolar bone, new bone formation of the periosteum, and root resorption [18]. Hartman et al. retrospectively investigated 114 patients with histiocytosis X who had oral involvement. They found that jaw swelling and a palpable mass were the most common soft tissue manifestations. Other presenting symptoms were mobility of adjacent teeth and pain [19].

In our case, there were no signs of aggressive alveolar bone destruction on either the right or left side of the mandible in the radiograph that had been taken 2 years earlier, nor was there bone loss distal to the right maxillary canine. Repeating the OPG revealed geographic bony destruction of the maxilla and both sides of the mandible, with the teeth appearing to float. This shows that taking dental radiographs serves to not only evaluate general dental health but also as a baseline record with which to monitor the development, progress, and aggressiveness of bony lesions of the jaw. Our patient is undergoing intralesional steroid injections, which have produced positive outcomes in several cases of mandibular LCH [20].

Lesions of the gingiva, jawbones, and teeth are seen as the first manifestation or a complication of LCH [21]; therefore, dentists can play an important role in the early detection and treatment of the disease, which would lead to better management.

According to the International Histiocyte Society Registry, 68% of adults with LCH had involvement in more than 1 system. Thus, dentists have a responsibility to refer patients with symptoms of LCH to a physician for a thorough systemic evaluation for possible multiorgan involvement [4].

Conclusions

Although rare, LCH should be considered in the differential diagnosis when an OPG shows "floating teeth." In such cases, full-body imaging must be performed to check for lesions in other organs. Therefore, treating a patient without taking a current dental radiograph that includes OPG can lead to misdiagnosis, delayed diagnosis, and mismanagement. Early diagnosis of LCH will not only prevent the progression of the disease but also avert further complications.

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