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Diagnostic Characteristics of Langerhans Cells Histiocytosis: Case Presentation and Literature Review

SUMMARY

Langerhans cell histiocytosis (LCH) is a rare group of diseases that primarily affects children but can also occur in adults, presenting with diverse clinical and radiological manifestations. LCH involves the skull in approximately 51% of cases and the jaws in about 30%. Clinically, LCH may present as ulcerated lesions, gingival erythema, or swelling, accompanied by severe pain and increased tooth mobility. Poorly or well-demarcated, scoop-shaped unilocular or multilocular alveolar bone destruction represent the most characteristic radiographic features of LCH. While treatment options for isolated lesions include surgical curettage or excision, intralesional steroid injection, and radiation therapy, spontaneous regression have also been reported in some cases. This article presents the diagnostic characteristics of two male patients with LCH manifesting as isolated lesions involving both the maxilla and mandible. Additionally, spontaneous regression of LCH is discussed within the framework of the current literature, based on the post-biopsy follow-up of the second patient.

Keyword: Langerhans cell histiocytosis, adult patient, cone-beam computed tomography, spontaneous remission

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CASE REPORT (CR)
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Introduction

Langerhans cell histiocytosis (LCH) is a rare group of diseases caused by the abnormal proliferation and infiltration of Langerhans cells (immature dendritic cells) into various tissues and organs.[1] It is primarily a single-system disorder that frequently occurs in children aged 1-3 years, with a clinical presentation ranging from isolated bone lesions to more aggressive mortal forms.[2,3]

In adults, the incidence of LCH is as low as 1-1.5/million cases per year, and it affects the skull in approximately 51% and the jaws in about 30% of cases.[2,4-7] Clinically, intraoral lesions typically present as ulcerated areas, gingival erythema or swelling.[1,2] The most commonly reported radiological finding of LCH is unilocular or multilocular alveolar bone destruction with a characteristic scooped-out appearance and poorly or well-demarcated borders.[1,5,8] The radiological features of LCH may mimic those of other bone disorders, potentially leading to misdiagnosis. Therefore, a biopsy followed by an immunohistochemical examination is essential for establishing a definitive diagnosis.[3] During the immunohistochemical evaluation, the positivity of CD1a, CD207, CD68, and S100 surface markers on Langerhans cells is confirmative for the diagnosis of LCH.[4]

The treatment approach for LCH depends on the extent and distribution of the disease. In single-system involvement, isolated bone lesions can be managed mostly by surgical excision or occasionally intralesional corticosteroid injections, while topical corticosteroids are reserved for cutaneous lesions. In patients with multi-system involvement, chemotherapy including the use of methotrexate, prednisolone, vinblastine, and etoposide is recommended.[3,9]

In order to administer the appropriate and effective therapy for LHC patients, adequate evaluation of both the clinical and radiological findings of the patients is vital to reach the correct diagnosis. The resemblance of the findings to those of other disorders complicates this evaluation for the clinicians and may lead to misdiagnosis.

Within this context, two adult LCH patients who were initially misdiagnosed are discussed along with their clinical, radiographic, and immunohistochemical findings in the context of the current literature.

Case Reports

Case 1

A 44-year-old male patient was referred to the Outpatient Clinic of Oral and Maxillofacial Radiology with complaints of severe pain and burning sensation in the left mandible for one year, and multiple tooth losses within the same region. Medical and family histories were non-contributory, but the patient reported a smoking history of one pack/day for 15 years until one year ago. Intraoral examination disclosed an erythematous ulcerated area in the left mandibular posterior region, gingival dehiscence on the buccal root of #25, and severe mobility in teeth #24, 25, 27, 34, and 38 (Figure 1). Negative vitality responses were obtained from teeth 25, 27, 34, and 38 to the electric pulp test (EPT).

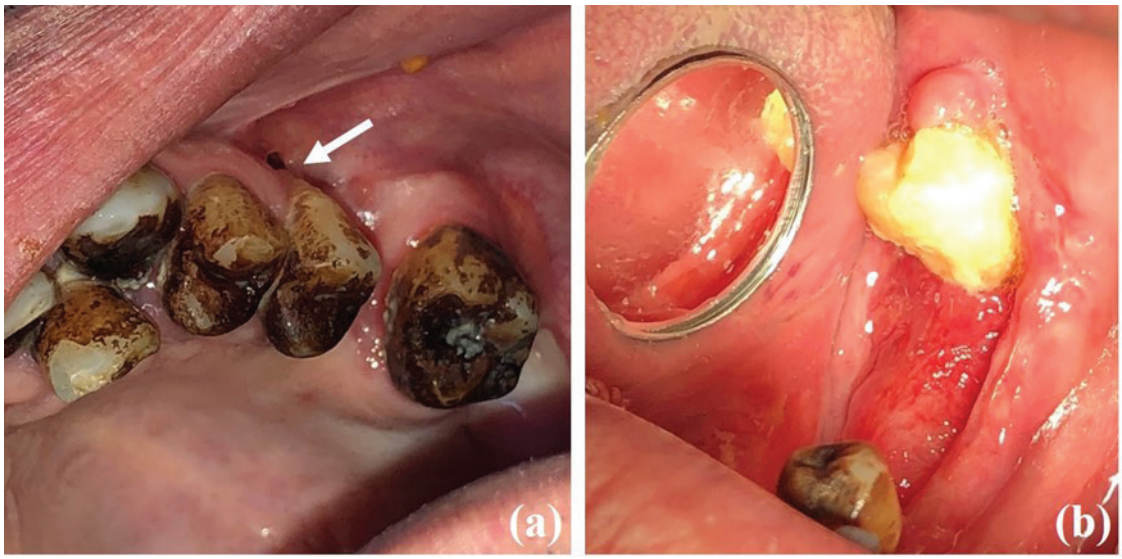

Figure 1. Clinical presentation of Case 1. Intraoral images showing (a) gingival dehiscence on the buccal root of #25 (arrow), (b) erythematous ulceration in the left mandibular posterior region.

During the extraoral examination, palpation of the left mandibular region revealed increased warmth accompanied by a tender, mobile, and hard submandibular lymph node and severe pain. Panoramic radiography (Figure 2a) and axial and sagittal cone-beam computed tomography (CBCT) sections (Figure 2d) revealed a 37 mm x 16. 3 mm destructive radiolucent lesion extending from the distal surface of #23 to the posterior of the tuber maxilla, resorbing the maxillary trabecular bone and the buccal and palatine cortical borders. Mucosal thickening was noted in the left maxillary sinus (Figure 2f). Axial and sagittal CBCT sections of the mandible disclosed a scooped-out-shaped radiolucent lesion beginning from the distal of teeth #33 and enlarging through the left posterior mandible (Figure 2b, c). The inferior alveolar canal was observed to be invaded by the lesion (Figure 2e).

Based on the clinical and radiological examinations performed at our department, a biopsy and a complete blood count were suggested with the preliminary diagnosis of LHC. In order to rule out hyperparathyroidism-related intraosseous jaw lesions, parathormone (PTH) and vitamin D levels were also questioned. PTH level was normal (32.13 ng/L, normal range: 15-65 ng/L), whereas vitamin D was close to the lower limit (20 ng/mL, normal range: 20-50 ng/mL). Blood count disclosed normal C-reactive protein (CRP) (3.15 mg/L, normal range: 0-5 mg/L) and sedimentation values (13 mm, normal range: <15 mm). In contrast to the clinical and radiological presentation of the patient, the histological diagnosis of the biopsy was “pyogenic granuloma”. Due to the lack of compatibility with the patient’s other findings, a rebiopsy was required. In hematoxylin and eosin (H&E) stained sections of the last biopsy specimen, diffuse Langerhans cell infiltration was detected, and immunohistochemical evaluation disclosed S100, CD207 and CD1a positivity in Langerhans cells (Figure 3).

Consequently, the patient received the final diagnosis of LCH and was referred for further bone marrow examination, which resulted as normocellular profile. Due to the multifocal involvement of the jaws and the risk of pathological fracture during surgical curettage, chemotherapy was planned for the treatment of LCH lesions.

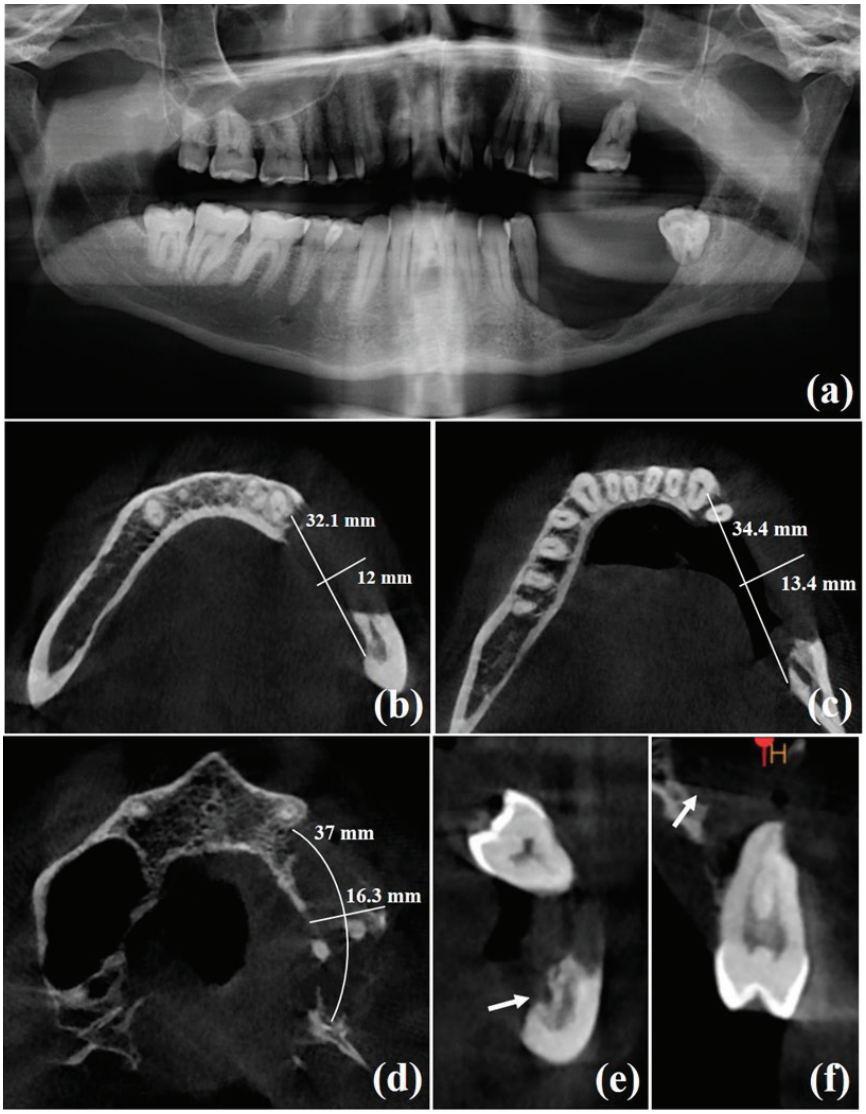

Figure 2. The radiographic aspect of Case 1. (a) Panoramic radiography showing scooped-out shaped bone destruction in left maxillary and mandibular posterior regions. (b, c) Axial CBCT sections revealing severe alveolar bone loss in the left mandibular posterior area. (d) Axial CBCT section of maxilla displaying extensive bone destruction in the left maxillary posterior region. Sagittal CBCT sections showing (e) the involvement of the inferior alveolar canal (arrow), and (f) mucosal thickening in the left maxillary sinus (arrow).

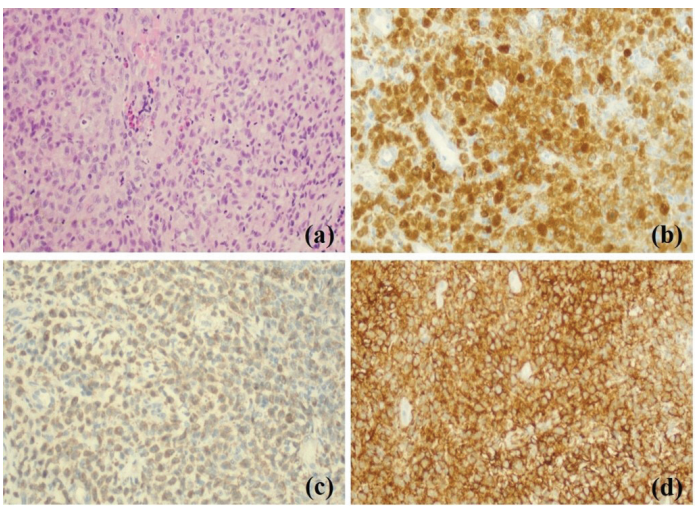

Figure 3. (a) Diffuse Langerhans cell infiltration and accompanying sparse eosinophil leukocytes (H&E). Immunohistochemical examination showing (b) S100, (c) Langerin and (d) CD1a positivity in Langerhans cells in (H&E, x20).

Case 2

A 57-year-old male patient was admitted to the outpatient clinic with severe pain in the anterior and left posterior mandibular regions and multiple spontaneous tooth losses in the left posterior mandible within one year. The patient had colon cancer that was diagnosed and operated in 2018, but he discontinued the chemotherapy voluntarily. The patient's family history was non-contributory, and he had utilized one pack/day of tobacco for over 15 years.

Intraoral evaluation displayed increased mobility in teeth #35 and 43. When EPT was applied to teeth associated with the lesion, positive responses were obtained from teeth #31, 32, 38, and 43, positive delayed responses from teeth #33, 34, and 44, and negative response from #45. Extraoral examination revealed that the left cervical lymph node was tender and mobile during palpation. Radiographic examination by panoramic radiography and CBCT revealed a scooped-out-shaped, ill-defined alveolar bone destruction in the anterior and left posterior mandible, extending from teeth #44 to 38 (Figure 4b, 4c-4e). The lesion was measured as 10.5 mm x 36 mm and 25.1 mm x 15.6 mm at the axial (Figure 4d) and sagittal (Figure 4f) CBCT sections, respectively. Periosteal new bone formation was detected in the anterior region of the mandible (Fig. 4g), along with external root resorption in tooth #31 (Figure 4h). The inferior alveolar canal was displaced to the lingual side (Figure 4i). In addition, a diffuse bone loss was also observed in the right maxillary posterior region (Figure 4b). When the panoramic image ordered in our department was compared with a previous radiograph from a different hospital one year ago, it was noted that the lesions had a rapid course of destruction (Figure 4a).

Based on the clinical and radiological manifestations of the lesions, the patient was referred for biopsy and a complete blood count with the preliminary diagnosis of LCH and bone metastasis. A high CRP level (5.39 mg/L, normal range: 0-5 mg/L) suggesting inflammation was observed in hemogram and the result of the initial biopsy was "pyogenic granuloma". Since it was not consistent with the findings of the patient, a rebiopsy was requested. After an immunohistochemical examination disclosing the diffuse infiltration of CD1a, CD207 and S100 positive Langerhans cells (Figure 5), the patient was diagnosed with LCH and referred for a bone marrow biopsy and PET scan. Bone marrow was 70% normocellular, and PET scan revealed hypermetabolic activity in the anterior and left posterior regions of the mandible and slightly increased FDG uptake in bilateral submandibular lymph nodes (Figure 4c1-4e1). A moderately increased FDG uptake was noted at the hepatic flexure of the colon, however, it was associated with physiological intestinal activity.

Seven-month panoramic radiography following the incisional biopsy revealed spontaneous regression and new bone deposition in the left mandibular posterior region (Figure 4j). However, due to multifocal lesions in mandibular anterior and maxillary right posterior regions, and increased FDG uptake in both mandibular anterior and posterior areas, radiation therapy was planned as the treatment of LCH lesions.

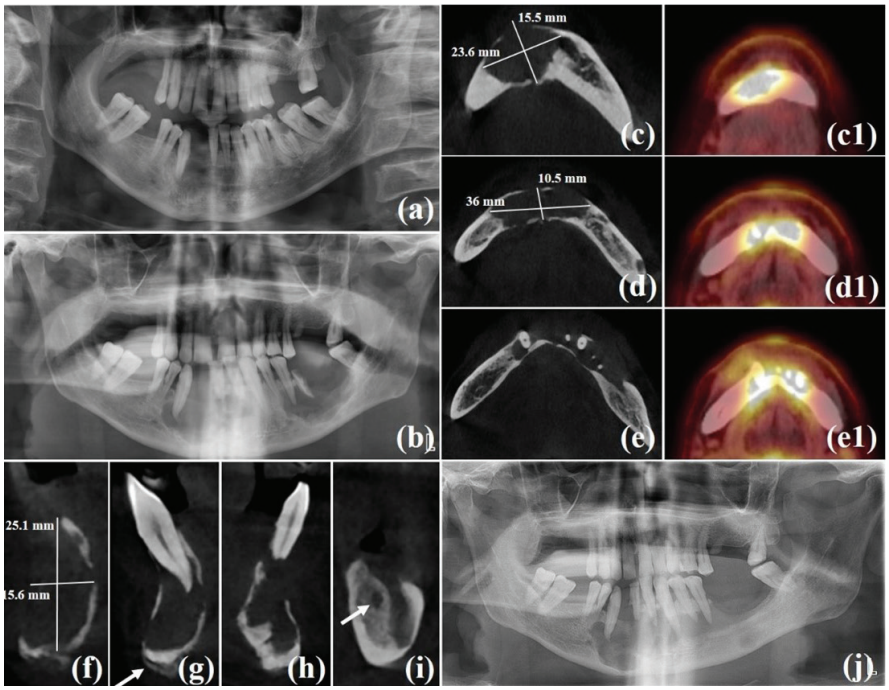

Figure 4. Radiographic presentation of Case 2. (a) Panoramic radiography image of the patient from one year ago. (b) Panoramic radiography taken at our hospital showing scooped-out-shaped and ill-defined alveolar bone destruction in the mandibular anterior and left posterior regions, and diffuse bone loss in the right maxillary posterior region. (c-e) Axial CBCT sections revealing the extensive bone destruction in mandible. (c1-e1) PET scan disclosing the hypermetabolic activity in the anterior and left posterior regions of the mandible. Sagittal CBCT sections of the mandible presenting (f) perforation of buccal and lingual cortical bones, (g) periosteal new bone formation in the anterior region (arrow), (h) external root resorption in tooth #31, and (i) lingual displacement of the inferior alveolar canal (arrow). (j) Panoramic radiography revealing spontaneous regression after the incisional biopsy in the left mandibular posterior region.

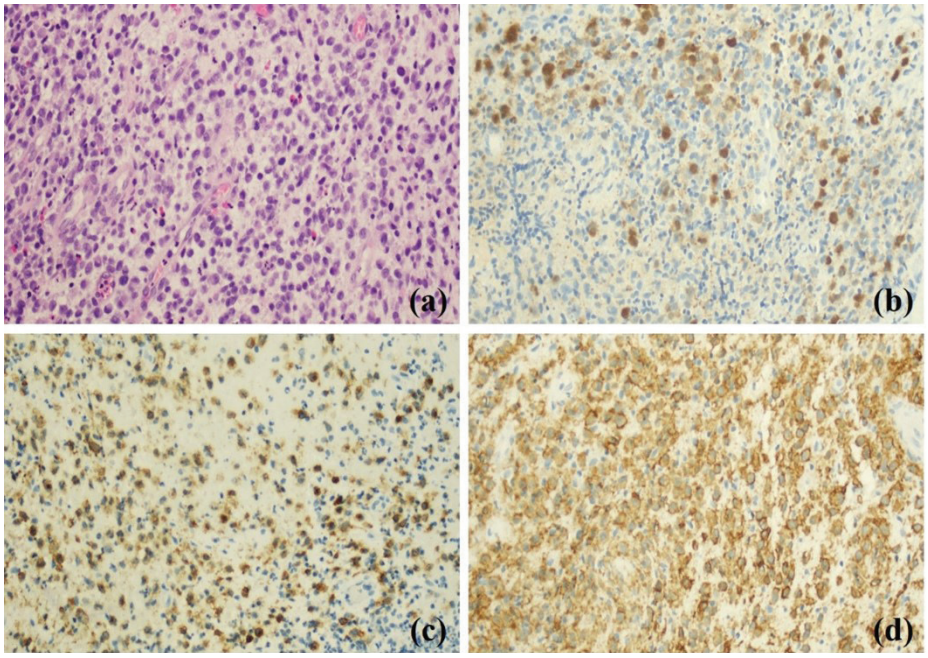

Figure 5. (a) Diffuse Langerhans cell infiltration and accompanying sparse eosinophil leukocytes (H&E). Immunohistochemical examination showing (b) S100, (c) Langerin and (d) CD1a positivity in Langerhans cells in (H&E, x20).

Discussion

Adult LCH predominantly occurs as bone lesions in almost 80% of cases, and frequently involves skull, long bones, jaws, facial bones, pelvis and vertebrae.[4,8] In accordance with this, we reported two adult LCH patients with isolated bone lesions presenting as scooped-out shaped osteolytic bone destructions involving both jaws. However, the involvement of the skin, endocrine system, nervous system, lung, and lymph nodes has also been reported by different authors, as well as a high risk of mortality in relation to the involvement of the liver, spleen, and bone marrow.[3,6] Although oral mucosal lesions are reported to be rare, it is important to recognize oral manifestations since they may serve as early indicators of LCH.[4,9] According to the previous cases reporting isolated maxillary and mandibular bone lesions in adult LCH patients (Table 1), gingival swellings and painful mucosal or gingival ulcerations are common oral findings to be noted.[2,4,9-27] In the current study, a large, painful ulcerated lesion was detected in the mandibular posterior region of Case 1. However, it was not considered an early sign, as it coexisted with bone lesions at the time of the patient's referral.

Jaw involvement of LCH appears as unilocular or multilocular destruction of the alveolar bone presenting as a characteristic "scooped-out" shape, accompanied by increased tooth mobility, multiple tooth loss, and floating tooth appearance.[2,4] Irregular and ill-defined osseous lesions have also been reported by different authors.[5,9] Even though the cases presented in this report demonstrated radiographic characteristics similar to previous case reports, the results of the initial biopsies were inconsistent with the clinical and radiographic findings in both patients. As noted in earlier studies, oral manifestations of LCH can easily be mistaken for aggressive periodontal diseases due to their overlapping clinical and radiographic features including increased tooth mobility, deep gingival pockets and generalized alveolar bone loss.[9] Accordingly, it becomes imperative to avoid relying solely on non-specific clinical and radiographic findings during patient evaluation and to incorporate histopathological examination when the findings of the patient are suggestive of LHC. However, despite being the gold standard for definitive diagnosis, histopathological evaluation resulted in misdiagnosis in both patients in the current study. It has been reported that inflammatory infiltration detected in the histopathological specimens of LCH lesions may lead to misdiagnosis in these group of patients.[28] Accordingly, the failure of the initial biopsy results in the present study may be attributed to the inflammatory content of the biopsy samples. On the other hand, the misleading nature of the biopsy specimen raises the question of whether histopathological interpretation might have been more definitive if it had been accompanied by clinical and radiographic features of the case. In agreement with this, Cerroni et al.[29] and Aslan et al.[30] emphasized that diagnostic accuracy improves when clinical and radiological findings, along with detailed clinical descriptions, accompany the biopsy specimen. Therefore, further studies should consider supplying the pathologist with more comprehensive information about the concerned lesion to improve diagnostic accuracy.

Immunohistochemical confirmation of CD1a, CD68, CD207, S100 antigens and Birbeck granules by incisional

or excisional biopsy is required for the definitive diagnosis of LCH.[3] Even though CD1a antigen expression is indicative for the diagnosis, it is not a specific marker for LCH, since CD1a may be expressed in some Non-Langerhans cell histiocytic disorders such as juvenile xanthogranuloma, sinus histiocytosis, and histiocytic sarcoma.[2] Therefore, CD207 positivity may be beneficial in leading the diagnosis, as it may point out the presence of Birbeck granules in Langerhans cells.[31] In the present study, S100, CD207, and CD1a positivity in Langerhans cells was confirmed with the immunohistochemical examination for both cases. Hence, the final diagnosis was LCH in both patients. Apart from the periodontal diseases, differential diagnosis of LCH should also include odontogenic cysts and tumors, benign and malignant bone lesions, metastases, multiple myeloma, giant cell granuloma and lymphoma.[4,32] Furthermore, in pediatric patients, different systemic disorders or syndromes such as Papillon Lefévre syndrome, hypophosphatasia, and cyclic neutropenia should be ruled out since they include clinical symptoms similar to LCH, such as premature tooth loss.[32]

Bone marrow involvement in LCH patients is associated with cytopenia and a higher mortality risk.[3,33] In LCH cases, the bone marrow may range from normocellular to hypocellular, and bone marrow involvement can be revealed by the positivity of marrow CD1a and CD207.[33,34] In this study, both cases were normocellular, and marrow CD1a and CD207 were not detected in the bone marrow evaluation of either of the patients. Considering severe or multi-system LCH patients tend to show more frequent marrow CD1a positivity than single-system LCH patients as the cases in the present study, this is a reasonable result.[33]

Table 1. Reported cases of LCH in adult patients with isolated jaw bone lesions involving both maxilla and mandible.

Author	Year	Age/Gender	Location	Clinical Findings	Radiological Findings	Histopathological Findings
Uckan et al.[10]	1996	26/M	Mandible, right maxilla	Aggressive periodontal disease, halitosis	Severe bone resorption, Floating tooth appearance	None provided
Kessler et al.[11]	2001	43/F	Mandible, maxilla	Non-healing ulcer, aggressive periodontal disease	Large cystic and osteolytic lesions	None provided
Marcos et al.[12]	2007	28/M	Mandible, maxilla	Teeth mobility, trismus, pain, swelling	Extensive bone loss, cystic lesions	None provided
Pontual et al.[13]	2007	28/M	Mandible, maxilla	Pain, teeth mobility, multiple tooth loss, facial asymmetry	Osteolytic scooped-out lesions, pathologic fracture	S100 and CD1a positivity
Rees&Paterson[14]	2008	31/M	Mandible, right maxilla	Pain, swelling, teeth mobility, exposed bone	Extensive bone destruction, punched out and scooped out lesions	Aggregates of histiocytes, S100 positivity
Lajolo et al.[15]	2012	71/F	Mandible, maxilla	Periodontal disease, erythematous mucosal lesion, gingival ulcers	Multiple uniloculate radiolucent lesions, cortical bone perforation	S100, CD1a and Langerin positivity
Terada[16]	2013	46/M	Mandible, maxilla	Facial asymmetry	Osteolytic lesions	S100 and CD1a positivity
Li et al.[17]	2016	22/M	Mandible, maxilla	Pain, swelling, gingival ulcers, teeth mobility, exposed bone	Cystic radiolucent lesions, ill-defined irregular radiolucency, scooped-out bone loss	Multinucleated histiocytes, numerous eosinophils
Altay et al.[18]	2017	26/M	Mandible, maxilla	Pain, teeth mobility, gingival enlargement with ulcerated and necrotic surfaces, halitosis	Extensive bone loss, ill-defined bone lesions	Langerhans cells, eosinophils, S100 and CD1a positivity
Salam et al.[19]	2017	22/M	Mandible, maxilla	Teeth mobility, multiple tooth loss, swelling	Severe bone resorption, multiple osteolytic lesions	Mononuclear Langerhans cells, CD1a, S100, and CD 45 positivity
Shaker et al.[20]	2018	25/M	Mandible, maxilla	Pain, swelling, gingival ulcerative enlargement, teeth mobility	Crater shaped bone resorption, severe bone loss, floating tooth appearance	Mononucleated histiocytes, eosinophils

Table 1. Reported cases of LCH in adult patients with isolated jaw bone lesions involving both maxilla and mandible (continuation).

Author	Year	Age/ Gender	Location	Clinical Findings	Radiological Findings	Histopathological Findings
Nangalia et al.[9]	2019	34/M	Mandible, left maxilla	Painless nodulo-papular and ulcerated gingival lesions, teeth mobility	Extensive alveolar bone loss	Langerhans cells, CD1a positivity
Bugshan et al.[21]	2020	42/M	Mandible, right maxilla	Teeth mobility, multiple tooth loss	Severe bone destruction, scooped-out shape lesions, floating tooth appearance	CD1a, CD68, and S100 positivity
Sabrine et al.[22]	2020	31/M	Mandible, maxilla	Pain, swelling, periodontal disease, teeth mobility	Severe alveolar bone loss, well-demarcated radiolucent lesions, pathologic fracture	Mononuclear histiocytic cells, CD1a positivity
Berberi et al.[23]	2021	42/M	Mandible, maxilla	Pain, swelling, gingival ulcer, gingival proliferation, teeth mobility	Well-defined radiolucent lesions, cortical destruction	Langerhans cells, acute and chronic inflammatory infiltrate
Xie et al.[24]	2021	35/M	Right mandible, left maxilla	Pain, gingival swelling, necrotic gingiva covered with pseudomembrane	Extensive bone loss, floating tooth appearance	Multinucleated histiocytes, eosinophils, S100, CD1a and Langerin positivity
Sreekumar et al.[25]	2024	23/F	Mandible, maxilla	Generalized gingival hyperplasia, gingival ulcers with punched-out borders	Generalized horizontal bone loss	Diffuse infiltration of histiocytes, CD1a positivity
Manhal et al.[26]	2025	63/F	Mandible, maxilla	Pain, generalized gingival hyperplasia	Horizontal bone loss, multiple periapical radio-lucency with inadequately defined and invasive margins	Proliferation of histiocytosis, polymorphic leukocytes CD1a and S100 positivity
Sood et al. [27]	2025	48/M	Mandible, maxilla	Diffuse gingival swelling	Extensive bone destruction	Foamy histiocytes, eosinophils, multinucleated large cells, CD1a and S100 positivity

Table 2. Reported cases of LCH showing spontaneous regression following the incisional biopsy.

Author	Year	Age/ Gender	Systemic Disease /Drug Use	Jaw Location	Additional Organ Involvements	Duration of Complete Healing Following Incisional Biopsy
Namai et al.[35]	2001	7/M	–	Mandible, right posterior	–	2.5 years
Key et al.[36]	2004	45/F	–	Mandible, right ramus	–	3 years
Baş et al.[37]	2011	7/F	–	Mandible, left posterior	–	10 months
Plona et al.[38]	2015	17/M	–	Mandible, right posterior	–	10 months
Vargas et al.[39]	2016	16/M	–	Maxilla, left posterior	–	9 months
Nezafati et al.[40]	2019	30/M	–	Mandible, maxilla	–	None provided
Khan et al.[41]	2019	11/M	–	Mandible, right posterior	–	3 years
Ono et al.[42]	2020	4/M	–	Mandible, left posterior	–	1.5 years

Treatment of LCH depends on the number of involved organs and the severity of the disease.[3] Surgical curettage or excision, intralesional steroids or radiation therapy are recommended for isolated lesions, while bisphosphonates, systemic chemotherapy or radiation therapy are suggested for multifocal bone lesions.[6,9] In terms of cases treated with surgical curettage or excision, total excision with clean margins is not suggested since excessive surgical intervention to the bone may affect bone remodeling.[3] Spontaneous regression and healing of LCH lesions following incisional biopsy of the patients without any systemic disease/drug use or additional organ involvement have also been reported by different authors (Table 2).[35-42] Despite of the cancer and chemotherapy

history of Case 2 in the present study, bone deposition was detected in the left mandibular posterior region on the 7-month follow-up panoramic radiograph after incisional biopsy. Although complete healing of the isolated jaw lesions has been reported between 9 months and 3 years, in the present study, radiation therapy was the treatment of choice for this patient due to persistent lesions in the mandibular anterior and maxillary right posterior regions, and his medical history.

Conclusion

Despite the low incidence of adult LCH, recognizing its clinical and radiological features is crucial due to the frequent risk of misdiagnosis. Adult LCH predominantly presents as bone lesions with jaw bone involvement in almost one-third of the cases. This study presented two adult cases of LCH involving maxillary and mandibular bone destruction, initially misdiagnosed as pyogenic granuloma based on preliminary biopsies, with definitive diagnosis established after subsequent rebiopsies. As demonstrated in our cases, when clinical and radiographic findings suggest LCH but biopsy results are not compatible with the histopathological diagnosis, a rebiopsy should be requested to reach a final decision. Furthermore, providing descriptive clinical and radiological images and information to the pathologist might be beneficial for preventing possible misdiagnosis and reaching a definitive diagnosis at once.

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