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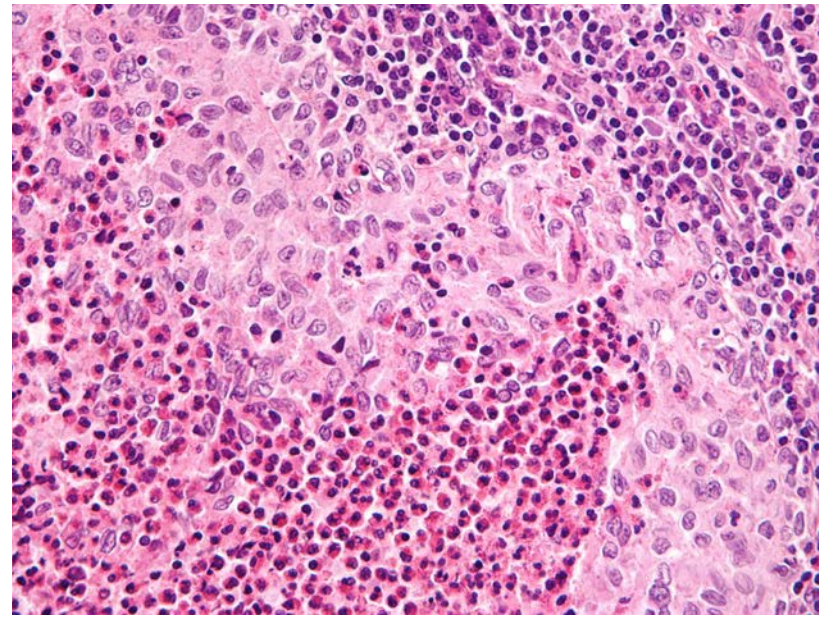
ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease of unknown pathogenesis that involves clonal proliferation of Langerhans cells and can affect multiple human body systems. LCH's presentation in the jaws is often mistaken for severe periodontal disease because of the bone loss pattern and attendant tooth mobility mimicking that of periodontal disease. The purpose of this article is to review the literature to highlight current diagnostic and therapeutic strategies for LCH in the jawbone. In addition, a case with spontaneous regression of an apparent isolated focal presentation of LCH in the mandible of a young man is presented. After performing a diagnostic biopsy, a conservative "wait and see" approach for treating LCH in jaws is suggested. Based on the available clinical evidence, monitoring of similar cases for a longer period is reasonable before drawing further conclusions.

EDUCATIONAL OBJECTIVES

Upon completion of this course, the dental professional should be able to:

1. Identify the dental and systemic clinical features of Langerhans cell histiocytosis
2. Distinguish LCH from periodontal and endodontic lesions
3. Describe the different modalities utilized for the management of involved teeth
4. Identify the team members who should be involved in treating such cases



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Langerhans cell histiocytosis of the jawbone—a lethal condition that might be mistaken for periodontitis

A comprehensive review and report of a case with spontaneous regression

A PEER-REVIEWED ARTICLE | by Hussein Basma, DDS, DESS, MS, and Muhammad H. A. Saleh, BDS, MS, MSD

Histiocytes, a type of cell arising from white blood cells, have a key role in regulation of immune functions and are typically involved in various aspects of host defense and tissue repair. A subset of histiocytes is Langerhans cells, which are dendritic cells that help in regulation of the immune system. They are usually found in various body regions such as bone marrow, the bloodstream, liver, lungs, and the pituitary gland.[1,2] Histiocytosis is a generic name for a group of syndromes characterized by a pathologic clonal proliferation of histiocytes.[3,4] When the disorder involves Langerhans cells, it is called Langerhans cell histiocytosis (LCH).[5-7]

Cells in LCH are mostly immature and can move into tissues where they are not normally found, causing damage in tissues such as skin, bone, lungs, liver, spleen, and lymph nodes.[7,8] In addition, these proliferating cells may form tumors called granulomas. This disease may range from a single lesion (solitary) to severe multisystem involvement, which tends to be fatal.[9,10] In up to 80% of the cases, one or more granulomas might develop in bones of the affected individuals, generally causing pain and swelling.[11] Granulomas occurring in the skull or long bones of the arms or legs may lead to bone fracture.[4,11]

The term Langerhans cell histiocytosis was presented in 1973, recognizing the key role of the tumor cells (Langerhans cells) in the disease.[12] By 1986, the Histiocytosis Association was founded, and since then it has established different standards regarding the definition, classification, and general management of LCH.[13] However, an ultimate definition of LCH continues to be disputed, mainly regarding its classification either as an immune dysfunction or a rare type of cancer (neoplastic and malignant or nonmalignant).[12,14]

The exact cause of LCH remains unknown. Many possibilities have been considered, including viruses, exposure to toxins, and geographic or familial links.[15] As mentioned earlier, many researchers believe LCH to be a form of cancer, yet numerous features suggest this disorder to be simply a reactive process or an immune system dysregulation.[16] This is portrayed through the characteristic inflammatory infiltrates of LCH, the benign morphology of its proliferating cells, and dysregulated expression of inflammatory cytokines, such as interleukin-17A,[17,18] and features such as spontaneous remission in lungs when smoking is stopped.[12] Inability of Langerhans cells to propagate in cell culture also fails to support a neoplastic nature.[19] In contrast, the neoplastic nature of this condition has been emphatically supported by demonstration of clonality,[19-21] with clinical manifestations ranging from solitary to multiple to disseminated progressive visceral, skin, and bone lesions. Lacking overwhelming evidence to support being a neoplasm, some have suggested that LCH is a distinct disease represented by clonal growth of immature Langerhans cells[22,23] that have mutations of the BRAF gene in almost 50% of the cases.[24,25]

Clinical features of LCH

The precise frequency of Langerhans cell histiocytosis in the adult population remains uncertain. Prior research, such as the study conducted by Baumgartner et al,[26] has provided estimates suggesting that the incidence of LCH in adults is relatively low, with about one to two cases per million.

LCH is known for its diverse clinical manifestations and outcomes. It can present as a self-limited localized disease, affecting a single area, or it can involve multiple sites within a single system. In some severe cases, it can even evolve into a life-threatening disseminated disease. This more severe form of LCH tends to involve multiple organs, including the skin, bone, liver, spleen, and bone marrow.[27]

However, there is a significant gap in our understanding of the incidence and survival rates of adult disseminated LCH (AD-LCH). Most of the clinical studies on AD-LCH have been limited to small series, as highlighted by Moravvej et al. in 2006[28] and Goyal in 2018.[29] Consequently, accurate estimates are lacking, underscoring the need for more comprehensive research in this area.

Oral health providers might be the first to see cases that present in jaws or head and neck soft tissues. The head and neck are the most common areas for LCH bone lesions to take place, with an incidence rate of 65% to 90%,[9,30-32] although the jaws are involved in 30% of adults but less than 10% of children.[33,34] The classic presentation

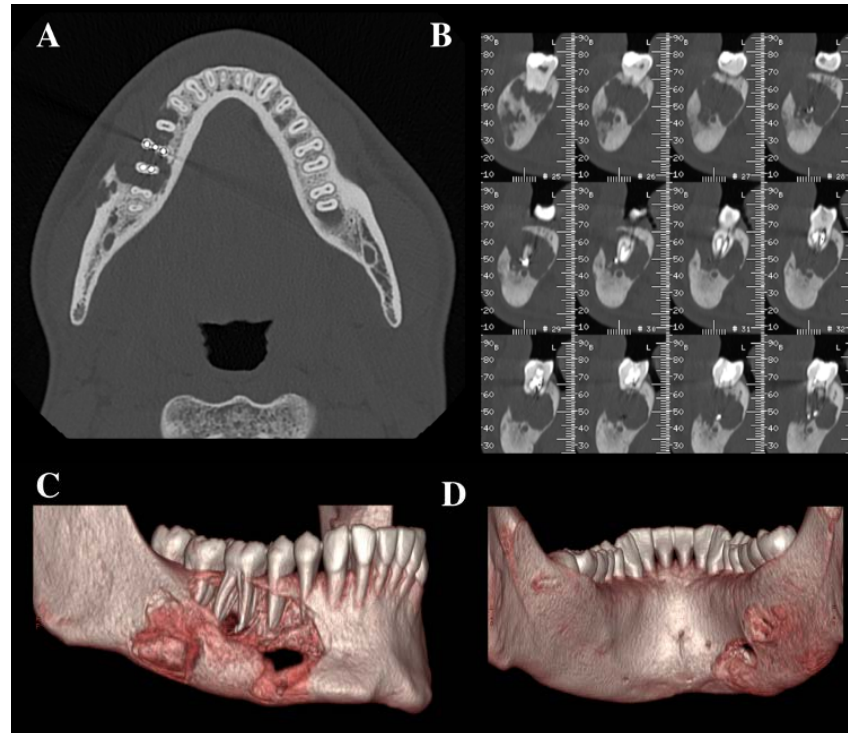

FIGURE 1: Multifocal osteolytic lesion of the jaw as it appeared at the time of the CBCT assessment

includes gingivitis, gingival hyperplasia, bleeding on probing, spontaneous bleeding, recession, necrosis, mucosal ulcerations, destruction of the alveolar bone and periodontal support, impaired healing, premature exfoliation of deciduous teeth, and early eruption of permanent teeth.[35,36] In adults, jaw lesions typically involve a mobile tooth with advanced bone loss. The presentation might resemble periodontal disease, odontogenic cyst, ameloblastoma, or other malignancies.[37-39]

Differential diagnosis

Often, LCH in jaws is accompanied by characteristic signs and symptoms of advanced periodontal disease, making its diagnosis more challenging as patients often spend considerable time mistakenly treated for periodontitis.[34,40,41] Periapical lesions are often misdiagnosed as periapical cysts or granulomas; a vitality test affirming pulp vitality should exclude this possibility. Other lesions may present in the ramus at the inferior border of the mandible, condyle, or any other facial bone simulating a sarcoma, osteomyelitis, or odontogenic neoplasm, others may have a multilocular radiographic appearance **(figure 1)**. Frequently, jaw lesions do not produce noteworthy symptoms except for mild bone pain, teeth mobility, or bony expansion.[42] Histologic examination of tissues removed for a biopsy using immunohistochemical analysis generally serves to differentiate LCH from other disorders listed above.

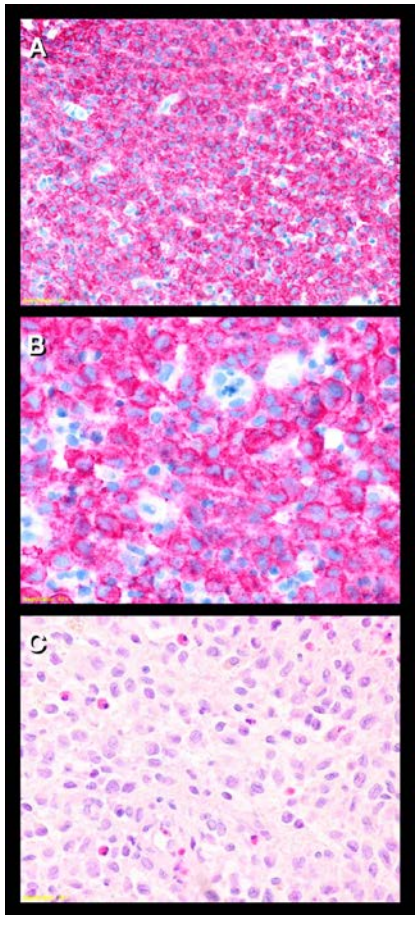

FIGURE 2: Histological examination revealed proliferation of medium- to large-size histiocyte-like Langerhans cells with large cytoplasm and irregular nuclei, with the presence of eosinophilic granulocytes and some lymphocytes. A diagnosis of Langerhans cell histiocytosis was made.

Diagnostic workup

LCH is generally considered to be underdiagnosed since some patients have minimal to no symptoms. Others are misdiagnosed for injury or different conditions due to the uncommonness of this disorder. In jaw lesions, diagnostic workup cannot be overemphasized due to the similarity of LCH to nonspecific periodontal inflammation. The radiographic appearance is quite variable and not specific[41,43] and changes with the phase of the disease.[41,44,45]

When LCH is suspected, a biopsy of the involved site is usually required (including involved teeth, if any). Once the biopsy is taken, the pathologist should be informed that LCH is included in the differential diagnosis. Histologic appearance does not necessarily correlate with behavior of the disease. A low-power view usually suggests an inflammatory process, characterized by the proliferation of Langerhans cells with the kidney bean-shaped nuclei (rentiform) appearance.[46,47] Inflammatory cells are also present (predominately eosinophils) and may include lymphocytes and neutrophils.

Another common feature is Birbeck granules **(figure 2)**, which are cytoplasmic structures that are rod shaped and have periodic striations that resemble a zipper, or in some instances resemble a tennis-racket shape.[7,15] Recognition of these granules in lesion cells using an electron microscope is pathognomonic, especially in more difficult cases. However, the diagnostic method of choice for pathologists is immunohistochemistry using CD1a antigen.[48] Typically, S-100 protein is also positive, although it is not specific for LCH.[49] Once a definitive diagnosis is reached via histopathologic examination, a skeletal radiographic survey and a thorough physical examination should be performed to determine the extent of the disease.[15,50]

Management

The challenges in management of LCH rest in determining the status of the disease, whether it is a reactive or neoplastic form of LCH. Management of LCH normally relies on the grade of systemic involvement and the age of the patient. Younger patients at the time of disease onset have poorer prognosis since LCH tends to be more generalized.[31] LCH is also known to generally be more responsive to a variety of treatments such as medications, surgery, and chemotherapy—either a definitive remedy or long-term palliation.[51] It should also be realized before delving into management details that some cases demonstrate a favorable nature, where disease regression occurs with minimal treatment.[52,53] Rarely, LCH may be unresponsive to therapy and may lead to death. Several treatment modalities have been proposed, such as curettage, surgical resection, radiotherapy, chemotherapy, intralesional steroids, and systemic steroids.[51,54,55]

Jaw lesions usually respond well to conservative treatment such as local

curettage. The lower the extension of bone lesions, the higher the chance the dentition has to be saved. Nonetheless, in most cases, alveolar bone resorption may result in substantial periodontal bone loss, imparting a "floating tooth" appearance **(figure 1)**. These areas rarely ever resolve, and bone loss becomes permanent. Therefore, it is often recommended to extract the involved tooth/teeth during biopsy/treatment.[42] For more invasive lesions, peripheral resection with a safety margin is recommended for all accessible jaw and facial bone lesions, including those in the skull.[55,56] For treatment of recurrent lesions or more extensive cases, the next line of treatment includes a myriad of options such as indomethacin, systemic steroid therapy, bone marrow transplantation, radiotherapy, bisphosphonates, and chemotherapy.[48]

Case report

In December 2015, a systemically healthy 24-year-old male presented to our clinic with extraoral swelling and slight tenderness in the posterior mandibular area. After clinical examination, the patient reported general malaise and occasional fever before the emergence of extraoral and intraoral signs. The patient's reported symptoms ranged from no pain to extreme pain accompanied by a swelling in the lower right molar area. On intraoral examination, mucositis and diffuse swelling at the mandibular right molar and premolar area were noticed. All molars and premolars in that quadrant were structurally sound and free of caries. Periodontal examination showed abnormal mobility in the first molar and second premolar with deep probing depths (>5 mm) without exudate. The first molar gave a negative response to a vitality test, while in the same quadrant, the second molar and both premolars gave a positive response. Intraoral periapical radiographs showed an apical radiolucency at the first molar. It was, therefore, decided to start the treatment with endodontic therapy of the first molar. Five canals were identified, explored, shaped, and irrigated with 5.25% sodium hypochlorite.

On the second appointment, in addition to concluding the root canal therapy, a more comprehensive approach was initiated for diagnostic purposes and to pinpoint the actual disease. Cone-beam computed tomography (CBCT) was performed and revealed multifocal radiolucent areas with irregular and ill-defined margins localized around the molar and premolar zone and below the mandibular canal, with the involvement of the inferior border of the mandible **(figure 1)**. The latter radiographic sign was a clear indication of an aggressive character of an osteolytic lesion. The images revealed a generalized multifocal radiolucency with an aggressive erosion of the lingual cortex of the inferior border of the mandible. Therefore, it was decided to perform blood analysis and an incisional biopsy to reach a definitive diagnosis.

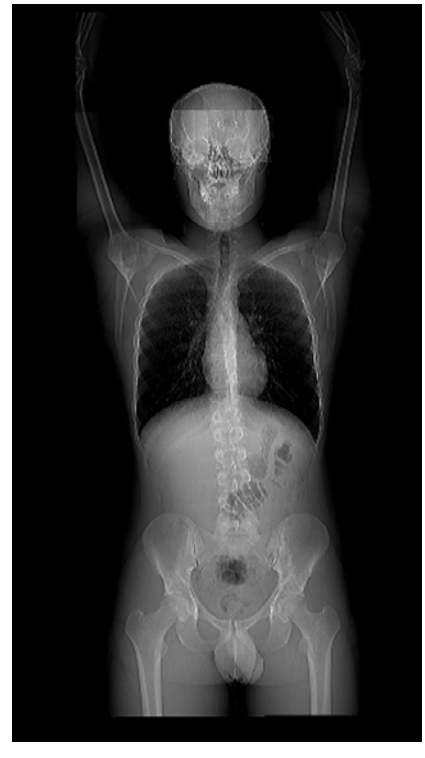

FIGURE 3: Full-body scan of the patient, showing no evidence of osteolytic change aside from the jaw

Hematologic analysis revealed normal values of the leukocytes and above standard values for erythrocyte sedimentation rate (Katz index = 16.5; normal values are 2-12) as well as a high alkaline phosphatase value (249 u/l; reference range of 98-179 u/l). Histological examination revealed proliferation of medium- to large-size histiocyte-like Langerhans cells with large cytoplasm and irregular nuclei, with the presence of eosinophilic granulocytes and some lymphocytes **(figure 2)**. The immunohistochemical characterization showed positivity for the CD1A and S100 markers. The K167/MIB1 was 10%. The semiquantitative evaluation of the mutated BRAF protein (V600E mutation) was negative (positive neoplastic population absent). By that time, the diagnosis of LCH was established. A full-body computed tomography (CT) was performed with and without contrast medium. No other organs were found to be involved in the disease **(figure 3)**.

With this diagnosis, a definitive treatment strategy was formulated involving surgical excision of the lesion with a safety margin. Based on the patient's wish, surgical therapy was postponed for seven months. During that time, the patient sought a second medical opinion and had his premolars and second molar root canal treated. Approximately three months after the last root canal therapy was performed (more than eight months from his first visit), the patient presented again to our clinic. Major signs of remission were observed when a follow-up CBCT scan was performed **(figure 4)**. After this unexpected incident, it was decided to follow a "wait and see approach" and recheck the lesion in another six months. In February 2017, an additional CBCT was performed; again, signs of improvement were observed **(figures 5 and 6)**.

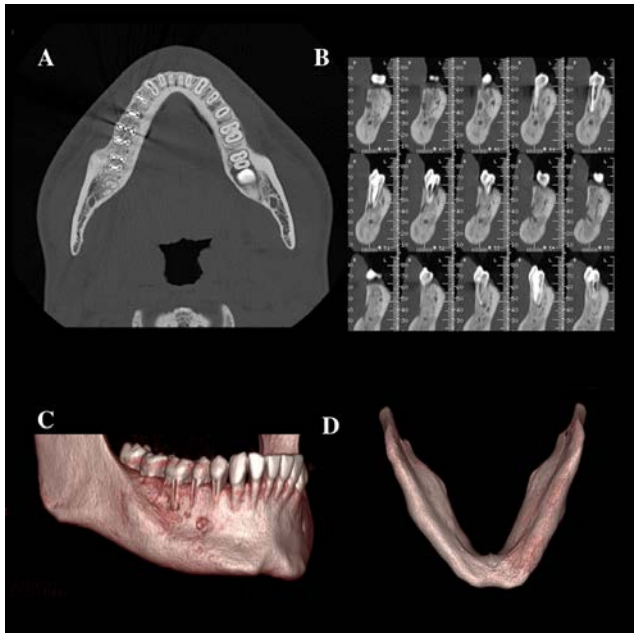

FIGURE 4: CBCT after seven months of follow-up; clear signs of remission can be noted

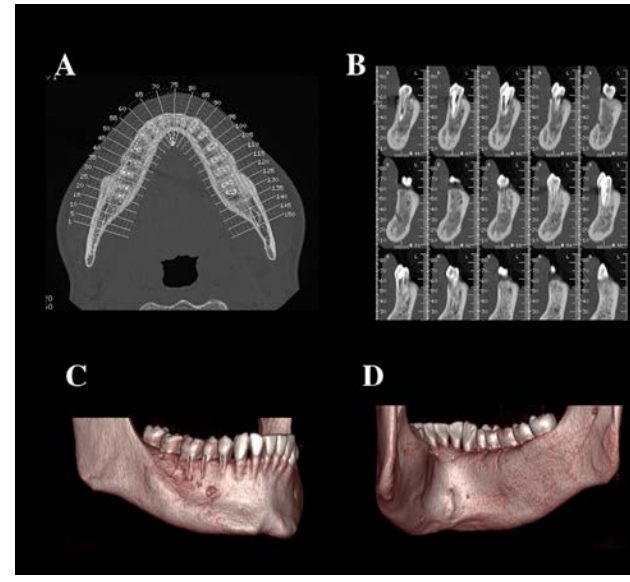

FIGURE 5: CBCT after two years of follow-up; total remission of multifocal osteolytic lesions is noted

Discussion

There is a good chance for the dental health-care provider to be involved in the recognition and diagnosis of an LCH lesion. If the discovered lesion is a late manifestation of a multisystem form of LCH, the dental care provider will be dealing with an individual whose physiology has been transformed by the animosity of the disease and its aggressive treatment modalities, including chemotherapy, radiotherapy, immunotherapy, and antiangiogenic therapy. That being said, the dental professional should be fully educated to be involved in the ongoing treatment process.

Prudent diagnosis is pivotal for LCH management. An LCH lesion mimicking a periodontal or periapical lesion will almost certainly cause delay in the diagnosis and treatment of the lesion. Performing an incisional biopsy might indeed be curative in LCH of the jaw. More importantly, the dentist should not have tunnel vision and solely treat the oral lesion, as these solitary lesions may present as an early sign of widespread LCH.[55,57]

A careful review of the scientific literature revealed that the elective treatment recommended for LCH in jaws is surgical curettage with or without associated steroid therapy.[52,58,59] Chemotherapy and radiotherapy have also been used successfully.[60,61] General recommendations specify that surgical intervention should be performed quickly, due to the rapid evolution and destructive capacity of maxillary lesions. However, chemotherapy has its own side effects, and while patients may be cured of LCH, they might not survive chemotherapy complications.[62,63] In addition, a surgical approach sometimes leads to a series of risks and complications.[61,64] It should be noted that treatment planning of this disorder is frequently influenced by occasional findings; this is why an analogous treatment is rarely reported in the literature.[39,57,65-67] Several other studies have shown spontaneous lesion remission,[53,59,60] remission after extraction of affected teeth,[52,68,69] or remission merely after performing an incisional biopsy.[59,66,70,71] Only one study attempted treating LCH in the jaw with indomethacin (NSAID), but LCH recurred after 21 months, when it was treated again with the same drug, proving to be successful only at that second attempt with a three-year follow-up.[49]

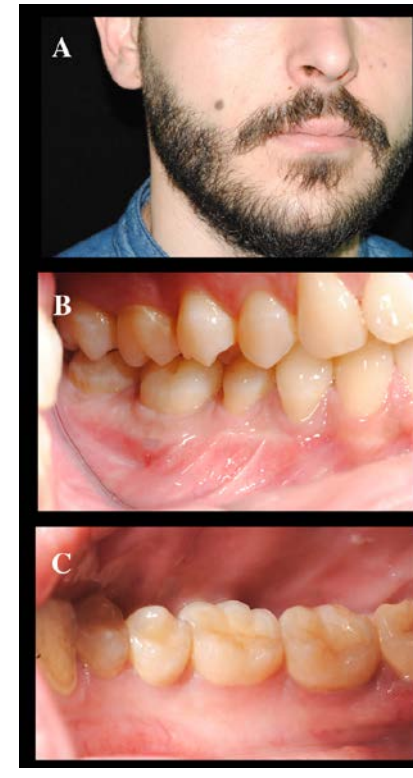

FIGURE 6: Extraoral and intraoral pictures of the patient after two years of follow-up

It is notable that in the case described here, following endodontic treatment of several teeth in the affected mandibular quadrant, the

osseous lesions regressed spontaneously. This phenomenon concerning endodontic or other local treatment in LCH of the jaw has been described repeatedly in the literature. It likely speaks to the fact that once the persistent inflammatory source is eradicated, the exaggerated/aberrant immune responses of LCH are no longer activated, and thus the LCH lesion is reduced.

It can be assumed that in select cases with similar characteristics, it may be possible to perform conservative treatment followed by strict follow-up prior to subjecting the patient to surgical therapy. It could be suggested that LCH of the jaw might be triggered by the presence of dental conditions that have an inflammatory etiology, capable of activating a mechanism that is not yet well known. The current case, along with several others, shows that once the source of inflammation is eliminated, the lesion could regress spontaneously.[18,59,69] In cases similar to the one reported, an interdisciplinary treatment approach should be implemented, involving several specialties such as hematology, oncology, and radiology, since the monostotic manifestation of LCH can be a borderline event.[61]

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1. What is the origin of histiocytes?
   - A. White blood cells
   - B. Red blood cells
   - C. Platelets
   - D. None of the above

2. Langerhans cells are ___ cells.
   - A. B lymphocyte
   - B. T lymphocyte
   - C. Dendritic
   - D. None of the above

3. Histiocytosis is a group of syndromes characterized by:
   - A. A decrease in the number of histiocytes
   - B. A pathologic clonal proliferation of histiocytes
   - C. A complete absence of histiocytes
   - D. None of the above

4. Cells in LCH are mostly ___ and ___ into tissues where they are not normally found.
   - A. Immature; can't move
   - B. Mature; can't move
   - C. Immature; can move
   - D. Mature; can move

5. What is the significance of Birbeck granules in the diagnosis of LCH?
   - A. They indicate the presence of an infection.
   - B. They are pathognomonic for LCH when recognized in lesion cells using an electron microscope.
   - C. They indicate the presence of a benign tumor.
   - D. They are indicative of a viral infection.

6. All of the following are possible causes of Langerhans cell histiocytosis except:
   - A. Viruses
   - B. Exposure to toxins
   - C. Geographic and familial links
   - D. Genetic absence of histiocytes

7. Which statement is correct concerning Langerhans cell histiocytosis?
   - A. The peak incidence occurs between 1-4 years.
   - B. Boys are affected more than girls with a ratio of 2:1.
   - C. A and B
   - D. None of the above

8. All of the following locations of LCH are considered to be at low risk except:
   - A. Pituitary gland
   - B. Liver
   - C. Bone
   - D. Skin

9. Which of the following is not a clinical feature of Langerhans cell histiocytosis?
   - A. It can present as a self-limited localized disease.
   - B. It can involve multiple sites within a single system.
   - C. It can evolve into a life-threatening disseminated disease.
   - D. It always results in severe pain and discomfort.

10. The ___ are the most common areas for LCH bone lesions, with an incidence rate of ___.
   - A. Arms; 70%-80%
   - B. Head and neck; 65%-90%
   - C. Lower extremities; 70%-90%
   - D. Head and neck; 5%-15%

11. Which of the following resembles the appearance of LCH?
   - A. Periodontal disease
   - B. Odontogenic cyst
   - C. Ameloblastoma
   - D. All of the above

12. Which of the following is not a potential cause of Langerhans cell histiocytosis?
   - A. Viruses
   - B. Exposure to toxins
   - C. Geographic and familial links
   - D. High blood pressure

13. LCH is generally considered to be ___ since some patients have ___ symptoms.
   - A. Underdiagnosed; minimal to no
   - B. Easily diagnosed; major
   - C. Overdiagnosed; absolute
   - D. None of the above

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14. A histological test of LCH is usually characterized by the proliferation of Langerhans cells with a(n) ___ nuclei appearance.
A. Oval-shaped
B. Kidney bean-shaped
C. Flat
D. None of the above

15. Which of the following could be present in the histological test of LCH?
A. Birbeck granules
B. Lymphocytes
C. Eosinophils
D. All of the above

16. Management of LCH normally relies on the ___ and the ___.
A. Grade of systemic involvement; age of the patient
B. Grade of local proliferation; sex of the patient
C. Location; age of the patient
D. Age; gender of the patient

17. All of the following are possible treatment modalities to treat LCH except:
A. Chemotherapy
B. Radiotherapy
C. Curettage
D. Antibiotics

18. The ___ the extension of bone lesions, the ___ chance the dentition has to be saved.
A. Lower; higher
B. Higher; lower
C. Higher; higher
D. Lower; lower

19. Which is not correct regarding treatment of LCH?
A. Jaw lesions usually respond well to conservative treatment such as local curettage.
B. It is often not recommended to extract the involved tooth/teeth during biopsy/treatment.
C. Peripheral resection with a safety margin is recommended for all accessible jaw and facial bone lesions.
D. Management is not dependent on the patient's gender.

20. For treatment of recurrent lesions or more extensive cases of LCH, what is the next line of treatment?
A. Indomethacin
B. Bone marrow transplantation
C. Systemic steroid therapy
D. All of the above

21. Which of the following is not a classic presentation of LCH?
A. Gingival hyperplasia
B. Spontaneous bleeding
C. Retained deciduous teeth
D. Early eruption of permanent teeth

22. The radiographic appearance of LCH is quite ___ and ___ with the phase of the disease.
A. Variable; changes
B. Rounded; remains the same
C. Variable; remains the same
D. Rounded; changes

23. Histologic appearance of LCH ___ behavior of the disease.
A. Correlates with
B. Does not necessarily correlate with
C. Is identical to
D. Is always contradictory to

24. All of the following are correct concerning Birbeck granules except:
A. Are rod shaped
B. Have periodic striations that resemble a zipper
C. Recognition of these granules in lesion cells using electron microscope is nonpathognomonic
D. In some instances, are tennis-racket shaped

25. General recommendations specify that a surgical intervention should be performed ___, due to the ___ capacity of maxillary lesions.
A. Quickly; rapid evolution and destructive
B. Later; slow evolution
C. Quickly; slow progression
D. As soon as possible, nonconcerning

26. Which of the following statements is true regarding LCH?
A. In a minority of cases, LCH can be life-threatening.
B. Oral health providers might be the first to see cases that present in jaws or head and neck soft tissues.
C. In adults, jaw lesions typically involve a mobile tooth with advanced bone loss.
D. All of the above

27. Younger patients at the time of disease onset have ___ prognosis since LCH tends to be more ___.
A. Poorer; generalized
B. Better; generalized
C. Better; localized
D. Poorer; localized

28. All of the following are considered to be high-risk locations except:
A. Bone marrow
B. Spleen
C. Liver
D. Lymph nodes

29. Which of the following is not a part of the diagnostic workup for suspected LCH?
A. Biopsy of the involved site
B. Blood tests
C. Histologic examination of tissues removed for a biopsy
D. Electrocardiogram

30. Which of the following affects chances of recovery and options available for treatment of LCH?
A. Extent of the disease
B. Whether risk organs are involved
C. How favorable the disease responds to initial treatment
D. All of the above

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Langerhans cell histiocytosis of the jawbone—a lethal condition that might be mistaken for periodontitis

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1. Identify the dental and systemic clinical features of Langerhans cell histiocytosis
2. Distinguish LCH from periodontal and endodontic lesions
3. Describe the different modalities utilized for the management of involved teeth
4. Identify the team members who should be involved in treating such cases

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5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	21.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
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9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	24.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	25.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	26.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	27.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	28.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	29.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	30.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

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