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Polyostotic Langerhans cell histiocytosis presenting as halitosis in a 24-year-old man: a case report

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Abstract

Background Langerhans cell histiocytosis is a rare disease of the reticuloendothelial system. This report presents a novel case of Langerhans cell histiocytosis with systemic involvement that started with a simple chief complaint. The reporting of this case raises awareness of the distinctive characteristics of this challenging disorder.

Case presentation A 24-year-old male patient of Persian ethnicity presented with a chief complaint of halitosis following coronavirus disease 2019 recovery to his general dentist's office. Intraoral and extraoral examinations revealed no specific problem. In the follow-up session after phase I periodontal treatment, teeth sensitivity to cold stimulus was evident, and radiographs revealed a large lytic intraosseous lesion in the mandible. An incisional biopsy revealed Langerhans cells and a positive reaction to Langerin and cluster of differentiation 1a, thus, he was diagnosed with Langerhans cell histiocytosis. After performing positron emission tomography with fluoro-2-deoxyglucose and computed tomography, magnetic resonance imaging, and cone beam computed tomography, owing to generalized disease involvement, the patient was referred to an oncologist. Ultimately, it was found that the patient's childhood health issues, including endocrine problems, were likely caused by an undiagnosed Langerhans cell histiocytosis. The oncologist chose denosumab, vinblastine, etoposide, 6-mercaptopurine, methotrexate, and pegfilgrastim regimen. The follow-up was not possible as the patient died following an accident.

Conclusion This reveals the vitality of the early diagnosis of Langerhans cell histiocytosis to prevent disease progression. Awareness of diverse and nonpathognomonic manifestations of Langerhans cell histiocytosis, proper medical interview and history taking, and the use of routine radiographs may aid clinicians in lowering morbidity and mortality rates associated with such conditions.

Keywords Polyostotic, Langerhans cell, Histiocytosis, Halitosis, Case report

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Introduction

Langerhans cells (LCs) are bone marrow-derived dendritic cells that are a crucial part of local immune response in the epidermis of the skin and the epithelium of mucosa. These cells are one of the antigen-presenting cells (APC) that process and present antigens to T cells and initiate an acquired immune response [1]. Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is an uncommon disease caused by neoplastic proliferation of LCs [2]. The term "histiocytosis X" was used and first described by Lichtenstein in 1953 [3]. The exact etiology of LCH is still unknown. The most frequent sites of intraosseous lesions are the skull, mandible, spine, pelvis, and femur [4]. Single or multiorgan damage may be seen in the liver, spleen, lungs, skin, bone marrow, central nervous system, and digestive tract [1, 5]. Clinical manifestation is characterized by various forms and stages. Oral manifestations of LCH might appear before signs elsewhere in the body. The most commonly affected site in the oral cavity is the molar area of the mandible [6]. The incidence of LCH is stated to be 3–5 per million; most of the patients are children below 3 years of age, and the incidence in adults is nearly 1–2 per million [7]. This case report presents a novel case of LCH with systemic involvement that started with a simple chief complaint (halitosis). However, further investigations and acquired data revealed LCH. It is noteworthy that the patient's childhood health issues, including endocrine problems, were likely caused by LCH. Reporting this case raises awareness of the distinctive characteristics of this challenging disorder that should serve as warning signs for physicians and dentists.

Case report

A 24-year-old man of Persian ethnicity presented with a chief complaint of mouth malodor after a period of mild coronavirus disease 2019 (COVID-19) recovery, which he wanted to resolve as soon as possible. His dentist noticed bone loss and bleeding on probing in the interproximal area of teeth numbers 18 and 19 clinically. Scaling and root planing was performed, and periapical and panoramic radiographs were ordered for patient evaluation. However, the patient refused to take radiographs. The patient's halitosis subsided after 1 week of treatment. After 2 months, patient returned to his dentist with the chief complaint of cold sensitivity in his mandibular incisors. The dentist performed a vitality test, and the teeth were vital except teeth numbers 23 and 24. The dentist took a periapical radiograph, and a radiolucent lesion in the anterior mandible was evident (Fig. 1).

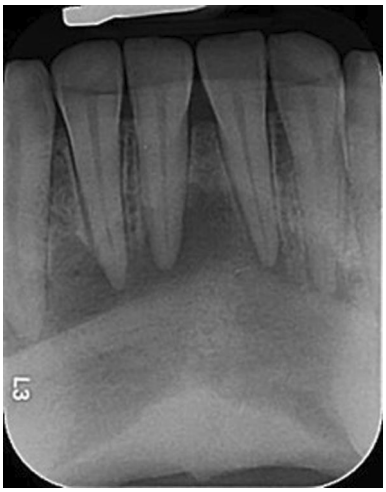

Fig. 1 Periapical radiograph from the anterior mandible

In panoramic radiograph, a large, well-defined lytic radiolucent lesion with scalloped borders extending from tooth number 31 on the right side to the left ascending ramus was evident (Fig. 2). Further cone beam computed tomography (CBCT) study revealed a large multilocular lytic lesion, with a relatively distinct margin, which caused thinning and perforation of buccal and lingual cortexes and signs of scalloping (Figs. 3, 4, 5, 6).

After examination, the patient was referred to an oral and maxillofacial surgeon. In the medical interview, the patient explained his mitral valve prolapse; history of recurrent episodes of otitis from the first year of his life; history of septicemia with an unknown origin when he was 1 year of age after episodes of diarrhea and vomiting; history of bronchodilator usage for seasonal allergy; history of levothyroxine, cabergoline, desmopressin acetate (DDAVP) spray, and testosterone gel usage for 4 years after diagnosis of empty sella syndrome following polyuria and polydipsia; and finally, a history of recent COVID-19 infection (3 months earlier). His familial history revealed Hashimoto's thyroiditis in his maternal family; his grandfather, mother, and all three of his aunts suffered from this kind of hypothyroidism. The patient's past surgical history included a repair of an inguinal hernia 10 years prior without any complications. In addition, the patient was obese, with a body mass index (BMI) of 34.5.

On clinical examination, extraoral and intraoral findings were unremarkable. Laboratory tests, including complete blood count (CBC), were normal, except for an increase in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. An incisional biopsy was performed in the anterior mandible, and the specimen was sent to the department of oral and maxillofacial pathology at the Shahid Beheshti University of Medical Sciences. Sections showed diffuse infiltration of large pale-staining cells such as histiocytes with indented and

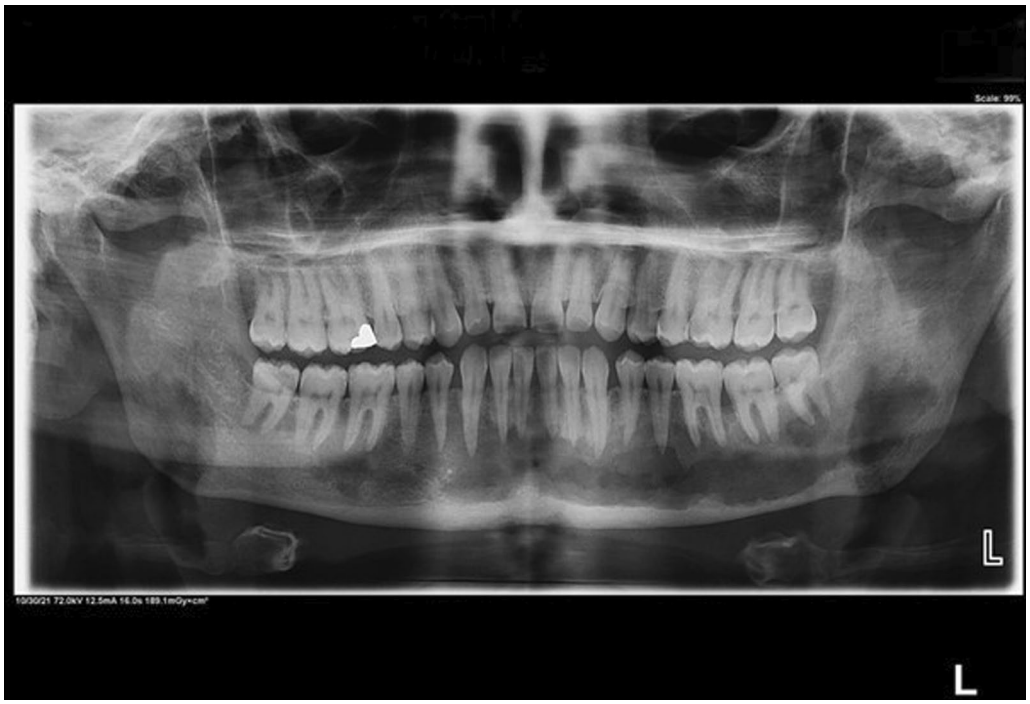

Fig. 2 Panoramic radiograph of the patient; A large well-defined lytic radiolucent lesion with scalloped borders evident

numerous eosinophils in the fibrous background (Fig. 7). An immunohistochemistry (IHC) examination revealed scattered positive for cluster of differentiation-1a (CD-1a) (++), strongly positive for Langerin (CD-207) (+++), and more than 50% positive for S-100 (Fig. 8A–C, respectively).

According to clinical, radiological, and histopathological data, the diagnosis of LCH was reached. Differential diagnoses were osteomyelitis, eosinophilic granuloma, and bone metastasis. However, owing to laboratory tests, radiologic data, and clinical history, the diagnosis of LCH was confirmed. Therefore, for further examination, the patient was referred to the nuclear medicine department for positron emission tomography with fluoro-2-deoxyglucose and computed tomography (FDG PET/CT), which revealed hypermetabolic lytic lesions in the mandible, right parietal, left frontal, and left sphenoid bones, and hypermetabolic opacity in the left ethmoid sinus. In addition, increased metabolic activity in the sellar region, communicating hydrocephaly, and prominent hypermetabolic palatine tonsils were observed (Figs. 9, 10). Moreover, heterogeneous-increased metabolic activity in bilateral tibia and femurs was evident (Fig. 11A, B).

A brain MRI revealed a remarkable enlargement of sella-containing cerebrospinal fluid (CSF) intensity material. Adenohypophysis appeared as a thin layer at the base of enlarged sella, and enhanced homogeneous and inflammatory changes were seen at the left mastoidal air cells. Extension of inflammation toward the left middle ear was seen (it is noteworthy that the patient suffered from otitis for many years). According to multifocal involvement of disease and its questionable prognosis, the patient was referred to the oncology department for systemic chemotherapy. Further tests revealed mutations in the *BRAF* oncogene and no detectable mutations in *KRAS* and *NRAS*. The oncologist chose a denosumab, vinblastine, etoposide, 6-mercaptopurine, methotrexate, and pegfilgrastim regimen; however, follow-up was not possible as the patient died following an accident.

Discussion

According to the literature, involvement with LCH could be either single-organ or multiorgan, but skin and bone have a higher involvement rate. Morphologically, LCH is composed of three similar lesions: eosinophilic granuloma, Hand–Schüller–Christian syndrome, and Abt-Letterer-Siwe syndrome [3]. Diabetes insipidus (DI) is the most common primary sign of central nervous system involvement in LCH [8], similar to symptoms of Hand–Schüller–Christian syndrome, which was seen in our case. Central diabetes insipidus, which persisted for 4 years, was determined to have been caused by the LCH. Still, the primary cause of the disease was unfortunately missed by the endocrinologist, who tried to solve the problem solely symptomatically. In case of inexplicable

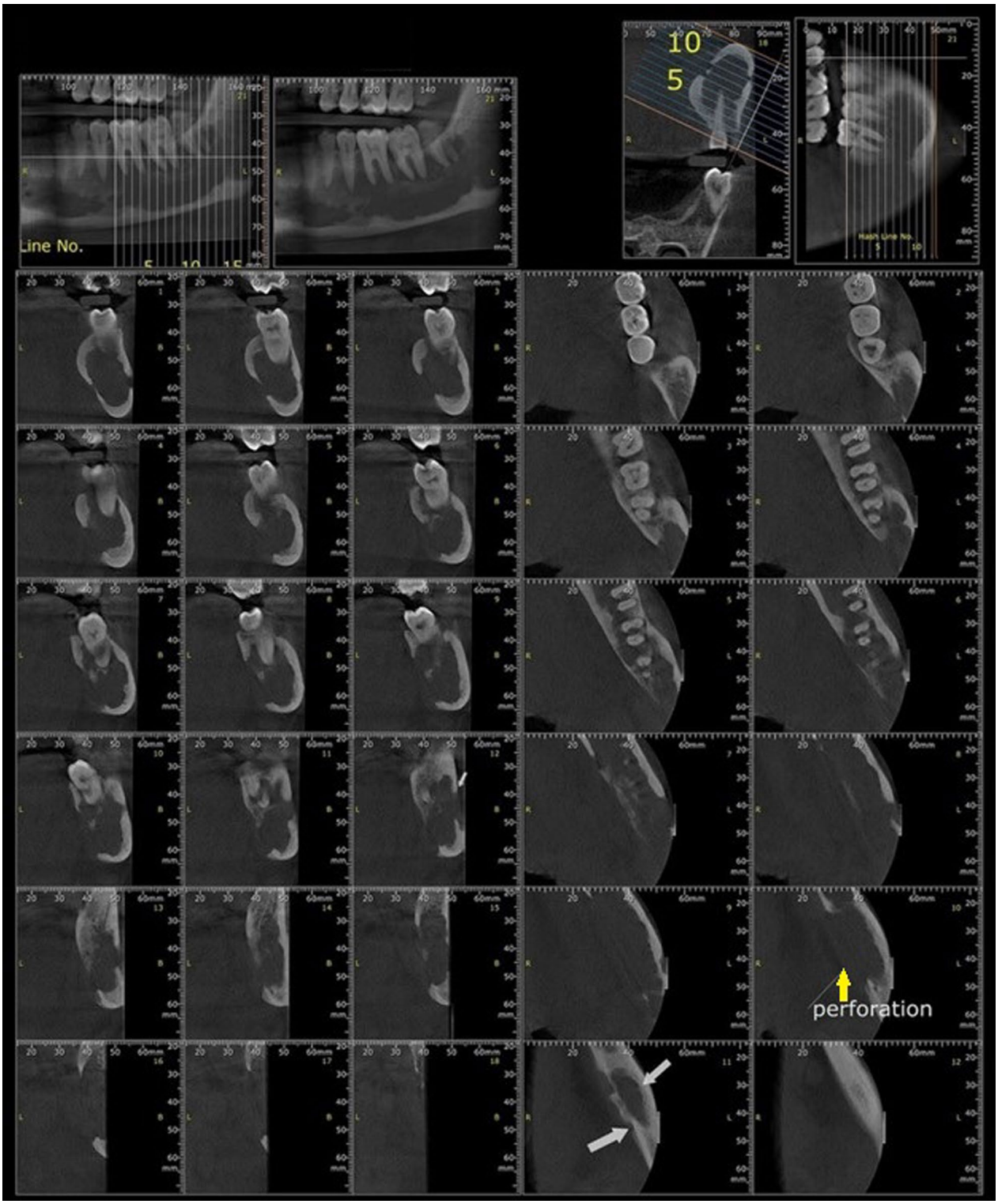

Fig. 3 Cross-sectional and axial cuts of left posterior mandible in cone beam computed tomography. The perforation in the lingual cortex (yellow arrow) and the lytic lesion in the base of the mandible (white arrows) are evident

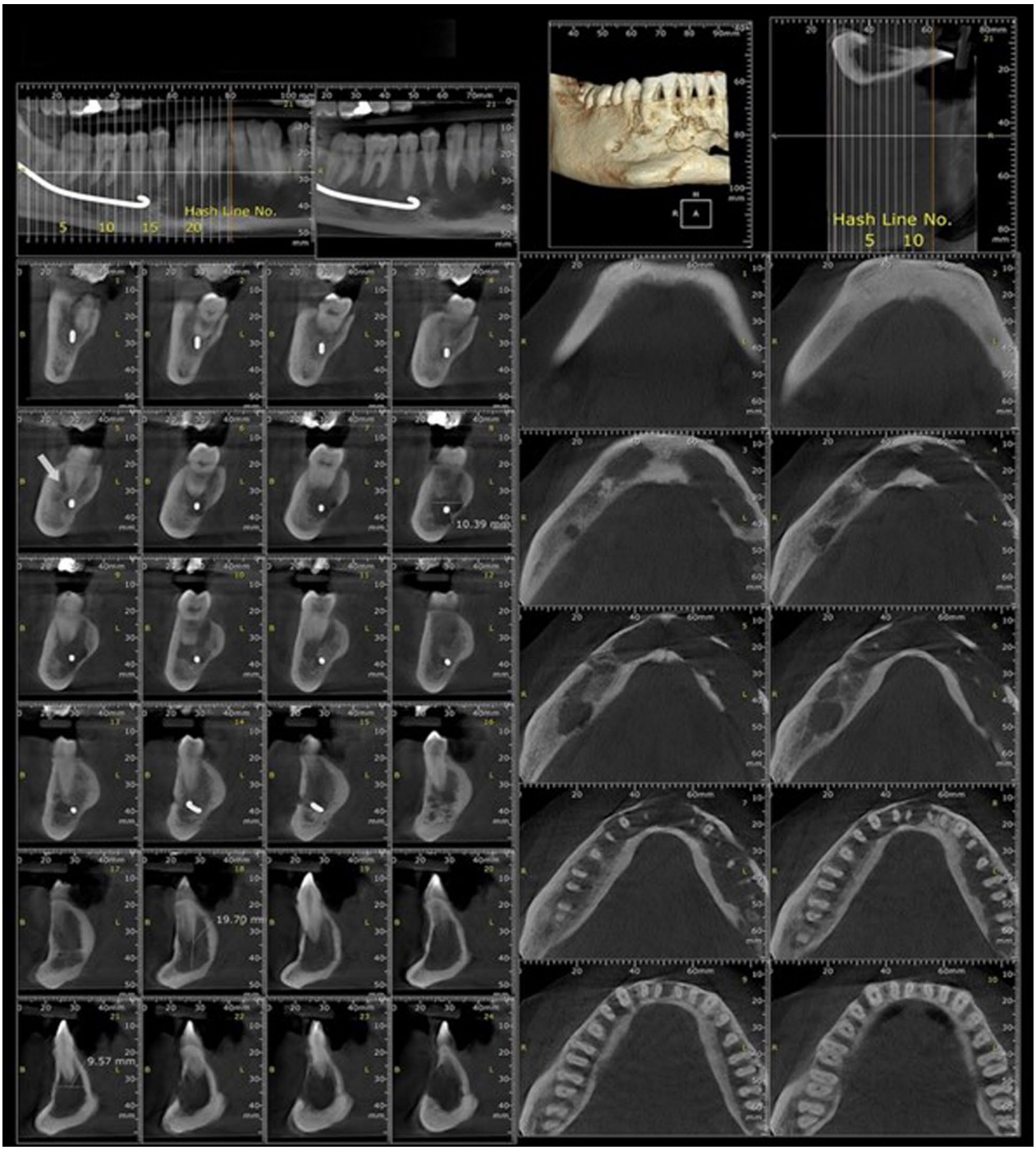

Fig. 4 Cross sectional and axial cuts of right and anterior mandible in cone beam computed tomography. The perforation is evident in lingual and buccal cortices

central diabetes insipidus or unclear lytic changes of the jawbone, LCH should be considered as a first differential diagnosis, and biopsy should be sought to reach a definitive diagnosis. The manifestations of LCH in the oral cavity may be pain, ulcerative lesions in mucosa, trismus, periodontal diseases, teeth mobility, swelling, nonhealing tooth extraction sites, and granulomatous [9, 10], but in our case, clinical examination only showed a mild, localized periodontal problem, although a huge bony lesion was present. Upon review of literature, there

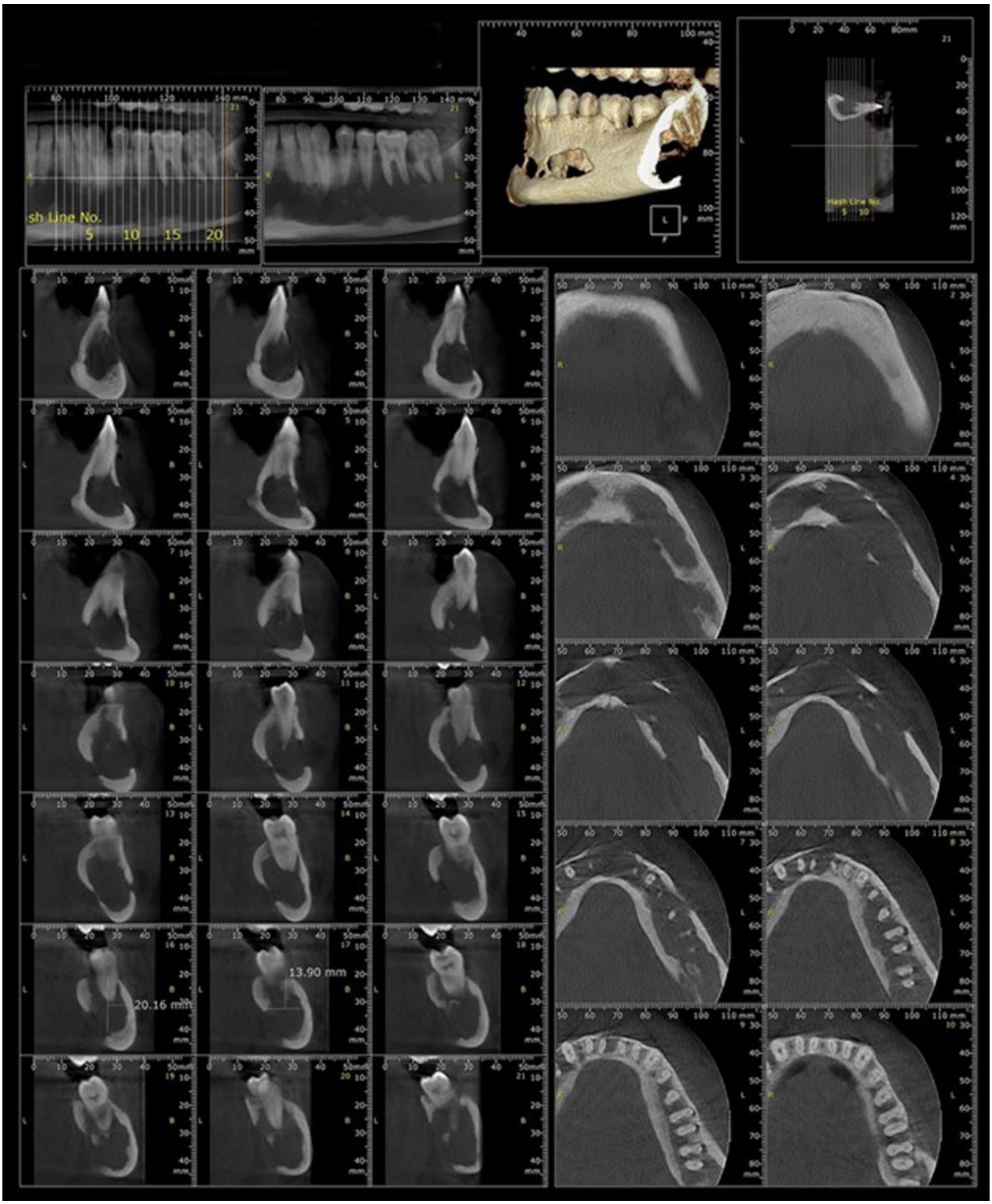

Fig. 5 Cross sectional and axial cuts of left posterior mandible in cone beam computed tomography

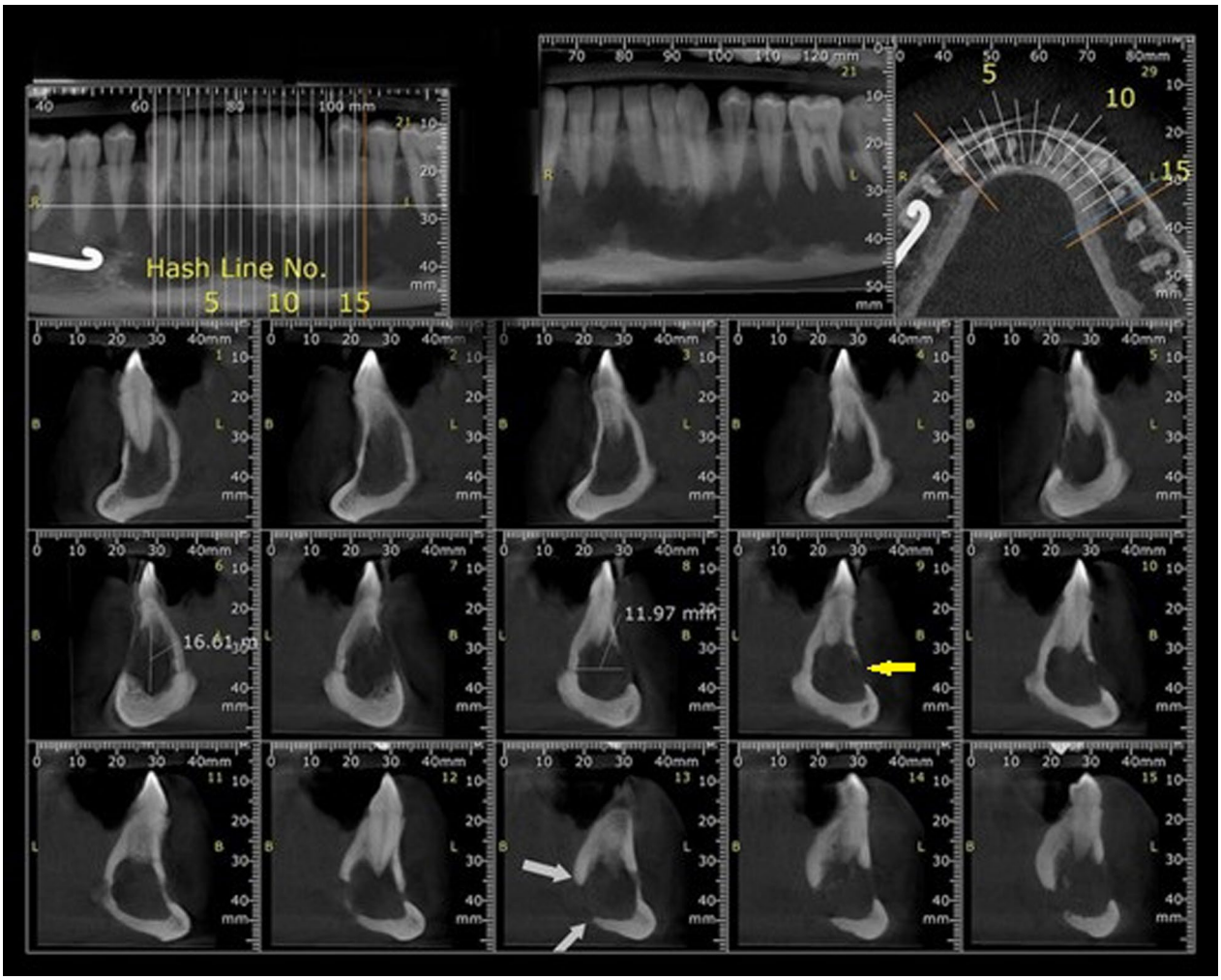

Fig. 6 Cross sectional cuts of anterior mandible in cone beam computed tomography. The perforation is evident in buccal cortex (yellow arrow) and lingual cortex (white arrows)

was no association reported between halitosis and LCH; however, our patient's chief complaint was halitosis. Isolated or generalized papules or eczematous lesions may be present on skin [11]. Our patient remembered recurrent eczematous lesions, especially in his axillary region, persisting for many years, but they were not present at the time of our study. Balaguruswamy and Chattington reported an unusual case of LCH with a history of involvement of the external auditory canal, and an empty sella on an MRI examination, which was treated with levothyroxine and testosterone; all of these were similar to our case, but their patient did not develop DI at the time of the study [12]. Stalemark and colleagues suggested that LCH is more commonly diagnosed during the fall and winter season as compared with the spring and summer season, which was similar in our case, as our patient was diagnosed in the fall [13]. Incidence is more prevalent in male patients than in female patients [14], which was consistent with our case. Studies have also shown a correlation between LCH and maternal

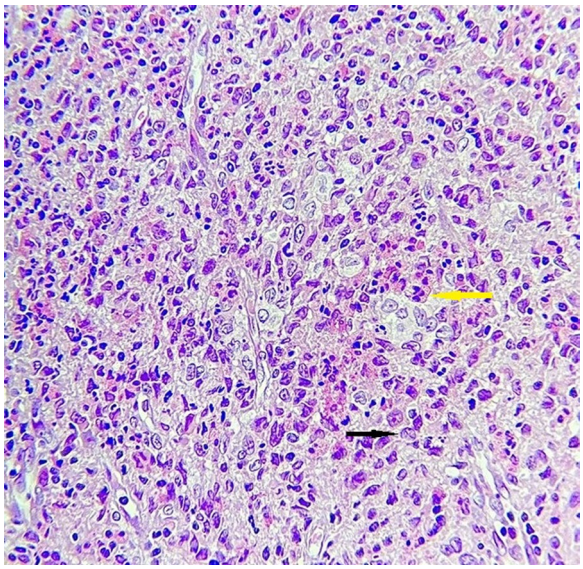

Fig. 7 Photomicrograph showing diffuse pale staining Langerhans cells intermixed with eosinophils; coffee bean-shaped histiocytes (black arrow) and eosinophils (yellow arrow) (hematoxylin and eosin stain, ×100)

and neonatal infections [15–18], lack of childhood vaccinations [15, 16], family history of thyroid disease [15], *in vitro* fertilization [19], feeding problems, and transfusions during infancy [18]. Our case had a history of severe early childhood infection and familial thyroid disease, but other problems mentioned above were absent. As far as we know, the patient's obesity might have been a manifestation of occult hypothalamic–pituitary LCH with delay in treatment [20].

On the nuclear medicine study, the disease pattern was similar to Erdheim–Chester disease (ECD). On IHC staining, ECD histiocytes are $CD68^{+}$, $CD163^{+}$, factor $XIIIa^{+}$, $CD1a^{-}$, and $CD207^{-}$ (langerin). Positivity for S100 is observed only in 20% of cases [21]. We know that LCs have myeloid origin, and more than 50% of them express BRAF V600E oncogene. In 25% of cases, mutations within the kinase genes, *NRAS* and*KRAS*, are observed, and our case was *BRAF* positive and *NRAS* and *KRAS* negative [22, 23]. Treatment plans for adult LCH include surgical curettage or resection, irradiation, local drug injection, and systemic chemotherapy. These approaches may be used either combined or alone. In the cases with focal bone lesion, surgical curettage or bone resection remain the best choices for treatment [24, 25]. Local radiation may be useful for relieving the symptoms, but complete remission is rarely achieved [26]. Local drug injections might be an effective treatment option for single-organ LCH. Libicher *et al.* reported cases of full remission of a solitary intraosseous lesion within 6 months following a single local injection of methylprednisolone [27]. Other studies addressed acceptable outcomes with intralesional steroid injections or indomethacin [28–30]. However, regarding a soft tissue lesion or multiorgan intraosseous lesions, systemic chemotherapy is often the first-line treatment plan [29], and finally, in our case, systemic chemotherapy was chosen.

Limitations of this study are significant, owing to the accidental death of the patient, which made the treatment and follow-up impossible. Moreover, whole-body imaging must be accomplished to explore for further lesions in other organs. Therefore, treating a patient without taking simple radiographs, such as panoramic view, can lead to misdiagnosis, delayed diagnosis, and mismanagement. Strengths of this study include thorough radiological evaluations, such as FDG PET/CT and MRI, and histopathological investigations, including IHC and genetic assessments.

Conclusion

This study documented the clinical, radiographical, and histopathological manifestations of a rare case of LCH in an adult. We should remember that LCH is a rare disease, and it is at risk of being under- or misdiagnosed. Thus, it is important to keep LCH in mind when dealing with

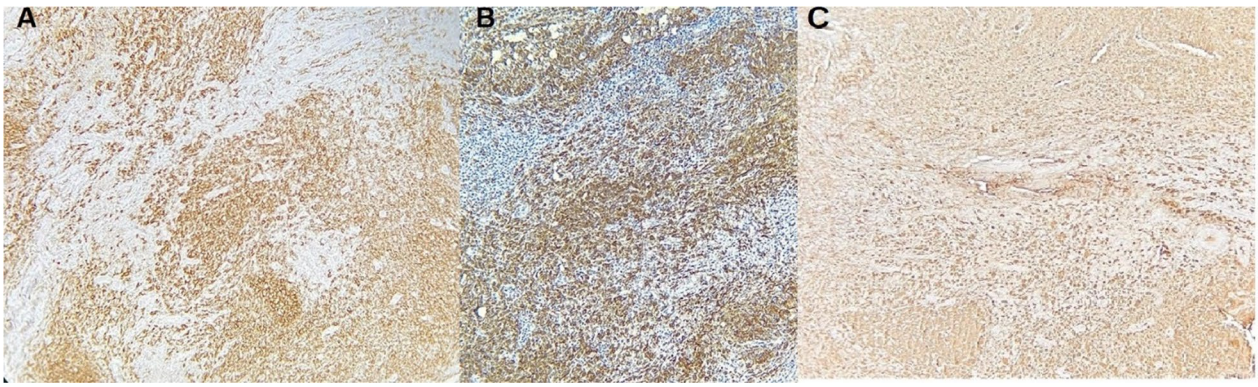

Fig. 8 Photomicrograph show reactivity of tumor cells for (**A**) cluster of differentiation-1a, **B** Langerin, **C** S-100 (immunohistochemistry stain, ×100)

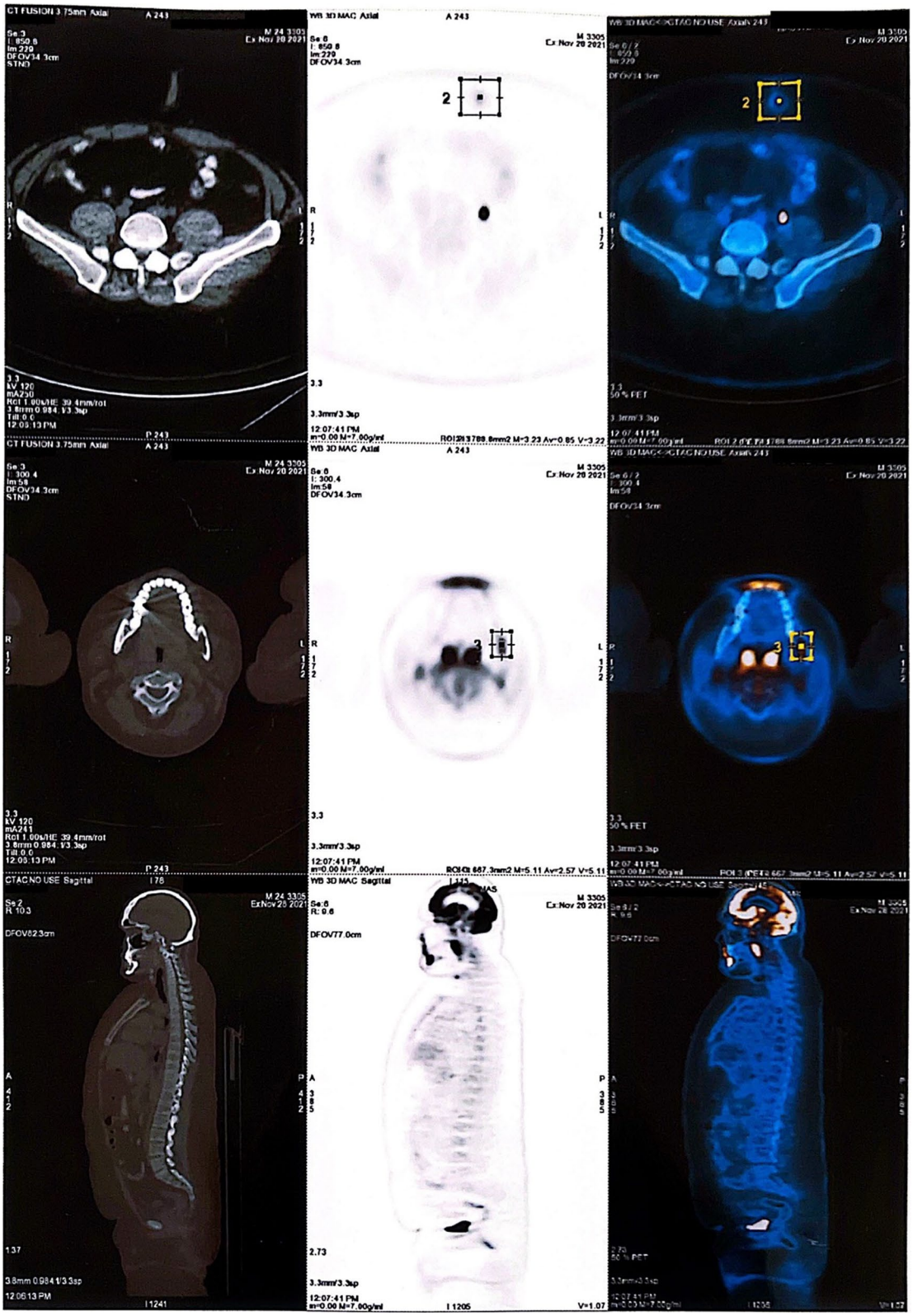

Fig. 9 Hypermetabolic lytic lesions in positron emission tomography with fluoro-2-deoxyglucose and computed tomography from vertex to mid-thigh. Prominent hypermetabolic palatine tonsils are evident

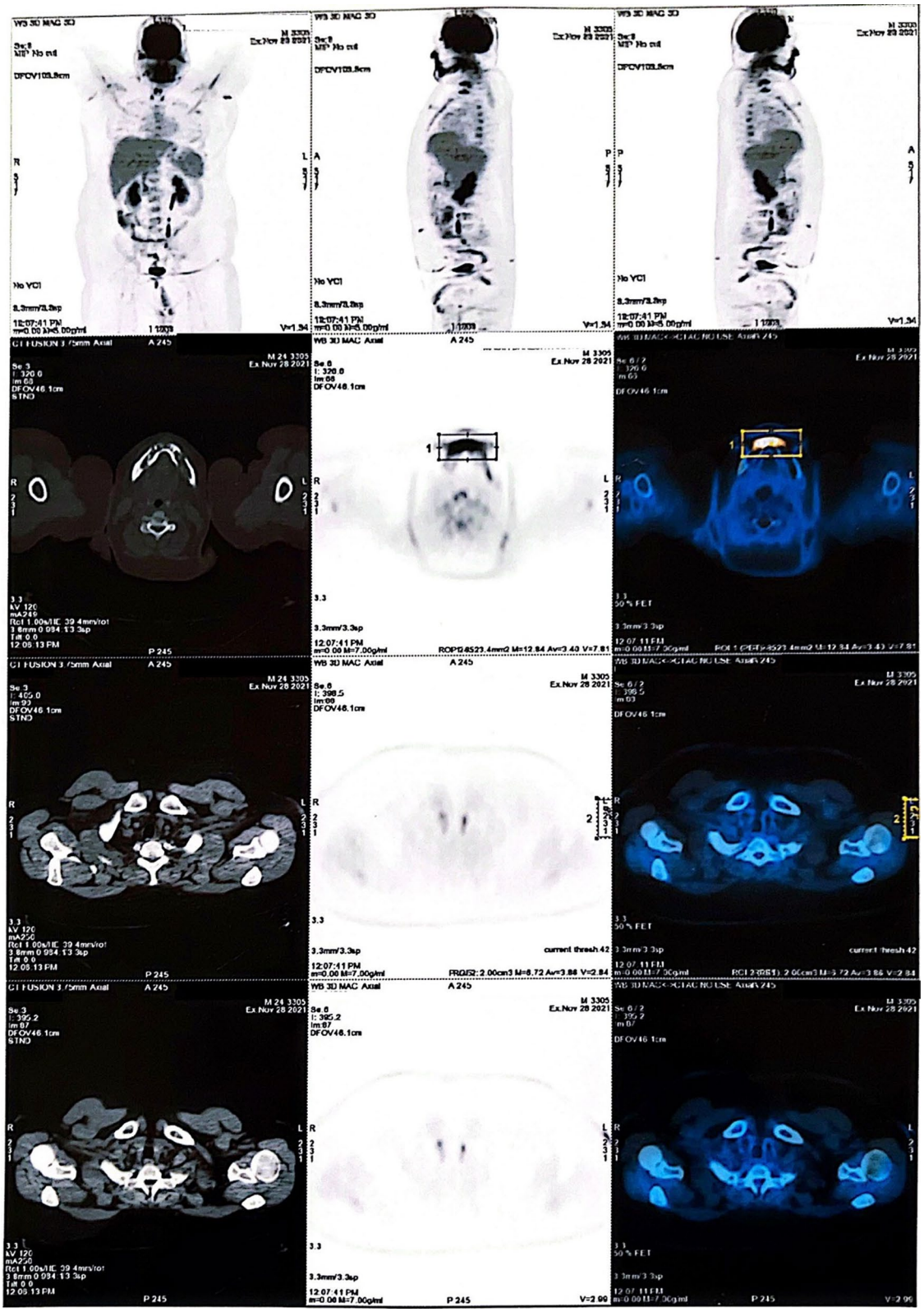

Fig. 10 Hypermetabolic lytic lesions in positron emission tomography with fluoro-2-deoxyglucose and computed tomography from vertex to mid-thigh. Prominent hypermetabolic lytic lesions in the mandible are evident

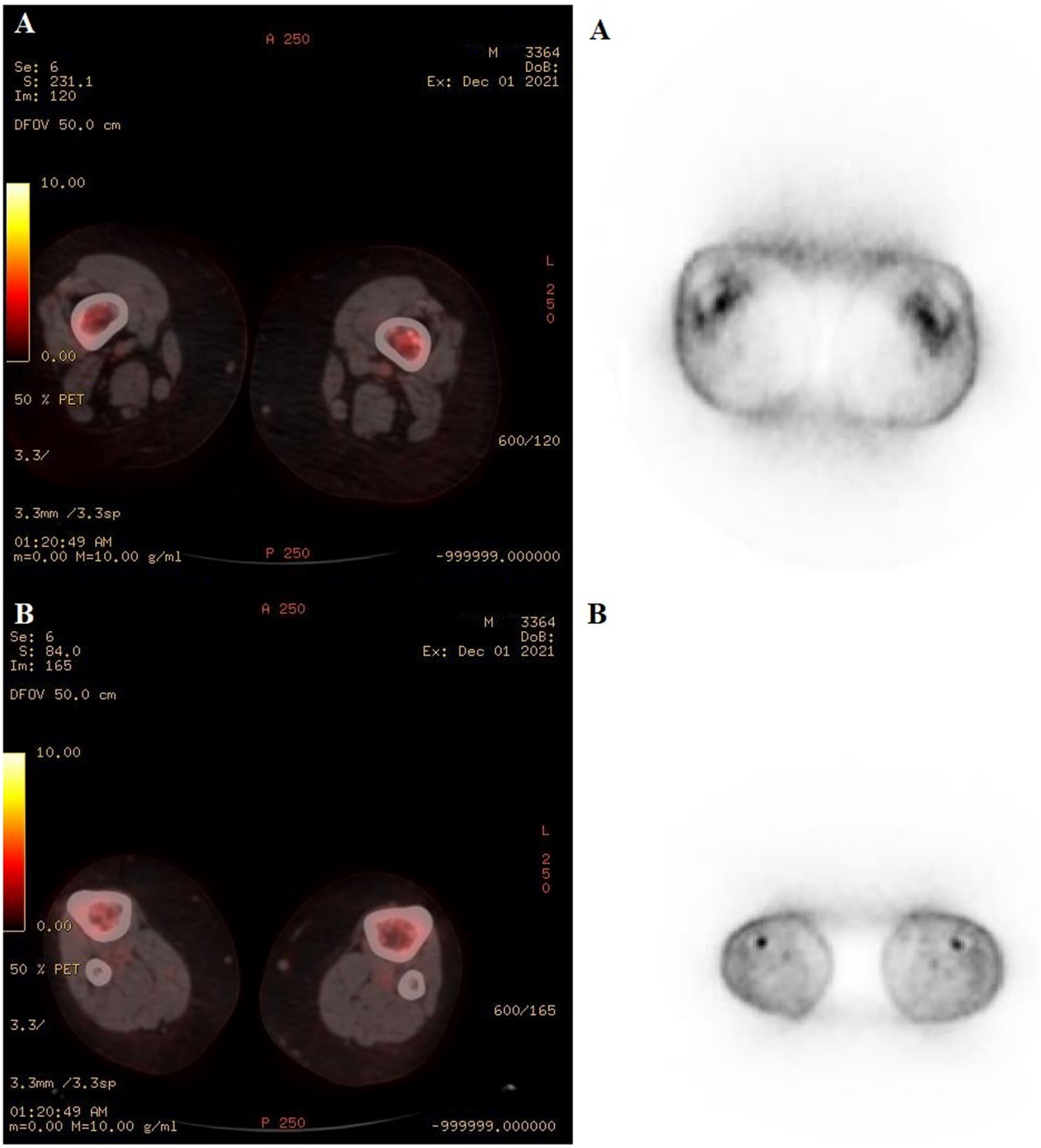

Fig. 11 **A** Increased metabolic activity in bilateral femurs **B** and tibia

unclear lytic bone changes, especially in the absence of a history of exposure to osteonecrosis-associated drugs, such as bisphosphonates. Early diagnosis of LCH will not only avert the development of the disease, but also prevent further complications. The nature of LCH necessitates a multidisciplinary method to be accomplished for precise diagnosis, an effective treatment plan, and an uneventful follow-up.

Abbreviations

LCH	Langerhans cell histiocytosis
CBCT	Cone beam computed tomography
FDG PET/CT	Positron emission tomography with fluoro-2-deoxyglucose and computed tomography
MRI	Magnetic resonance imaging
LC	Langerhans cells
APC	Antigen-presenting cells
DDAVP	Desmopressin acetate
ECD	Erdheim chester disease
BMI	Body mass index
CBC	Complete blood count
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
IHC	Immunohistochemistry
CD	Cluster of differentiation
CSF	Cerebrospinal fluid
DI	Diabetes insipidus

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Author contributions
The authors testify that all persons designated as authors qualify for authorship and have checked the article for plagiarism. If plagiarism is detected, all authors will be held equally responsible and will bear the resulting sanctions imposed by the journal thereafter. HMS was the principal designer of the work and the head of the research team. SG was the supervisor of the preparation of the manuscript and revised the scientific subjects of the manuscript. PN helped in gathering the medical data and in their interpretation. FM and MMC were the investigators of the tissue samples and helped with diagnosis, and MB and AKH were responsible for writing the manuscript and the grammatical revision of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Availability of data and materials
Further data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
There is no ethical issue.

Consent for publication
Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

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