Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

A challenging diagnosis of Langerhans' cell histiocytosis with hypothalamic-pituitary and mandibular involvement: case report and literature review

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Background: Langerhans cell histiocytosis (LCH) is a rare bone marrow derived neoplasm that mainly affects children. It is a multiorgan disorder and hypothalamic-pituitary involvement is uncommon. LCH reveals a wide spectrum of indications; thus, the diagnosis and treatment are usually challenging.

Case Report: A 22-year-old male presented with polydipsia, polyuria with nonspecific radiological findings, later on, developed a mandibular lesion and a biopsy was conducted which led to LCH diagnosis. After many improper treatments due to unclear diagnosis, the patient was finally placed on chemotherapy and is now under surveillance.

Discussion: LCH is a rare disease with diverse clinical manifestations affecting various organs. Associated mutations, such as BRAF V600E, contribute to its complexity. In adults, initial symptoms include pain, weight loss, and fever, with potential pituitary involvement leading to Arginine vasopressin (AVP) deficiency. Commonly affected organs include bone, skin, and the pituitary gland. The disease can be categorized into single-system and multisystem. Pathological diagnosis involves electron microscopy or immunohistochemical staining. Treatment options vary; the presented case utilized Desmopressin acetate and prednisolone before transitioning to cyclophosphamide for multisystemic LCH.

Conclusion: AVP deficiency can suggest hypothalamic-pituitary LCH, and a biopsy, if possible, is recommended to confirm the diagnosis.

Keywords: case report, Langerhans cell histiocytosis (LCH), mandible, polydipsia, polyuria

Introduction

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X (HX) or Hand-Schuller-Christian syndrome[1], is a rare abnormal clonal proliferation of myeloid dendritic cells (histiocytes or Langerhans cells) in the skin and visceral organs, which are immature, CD207 (langerin)-positive cells, derived from the bone marrow[2]. LCH is more common in childhood and rare in adults, with a predicted incidence of 1–2 cases per million and a peak prevalence between the ages of 20 and 35 years[2,3]. Yet the true incidence might be higher as it is commonly misdiagnosed[4]. It affects many organs and systems, especially the bone, skin, pituitary, liver, spleen, hematopoietic system, lung, lymph nodes, and central nervous system[5]. LCH has various symptoms depending on the affected system, leading to variations in diagnosis and treatment recommendations[1]. Furthermore, it has similar manifestations to many other diseases and no specific radiological findings; hence, a tissue-based diagnosis is essential to confirm the diagnosis of LCH. However, neither performing a biopsy is considered a gold standard due to its own limitations[6]. In this case, we discuss a unique manifestation of LCH involving the hypothalamic-pituitary region (HPR) and mandible bone lesions, highlighting the importance of biopsy in accurate diagnosis and effective treatment.

HIGHLIGHTS

- Langerhans cell histiocytosis is a rare clonal proliferation of myeloid dendritic cells.
- Underdiagnosis challenges in the hypothalamic-pituitary region, are highlighted in this case.
- A review of nine cases over the past decade revealed diabetes insipidus as the initial abnormality.

Clinical relevance:

- Langerhans cell histiocytosis should be considered in patients presenting with diabetes insipidus.

Case report

A 22-year-old unmarried Syrian male, a smoker and serving in the military, presented to the outpatient dental clinic with pain

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:4191–4196

Received 22 March 2024; Accepted 2 May 2024

Published online 15 May 2024

http://dx.doi.org/10.1097/MS9.0000000000002160

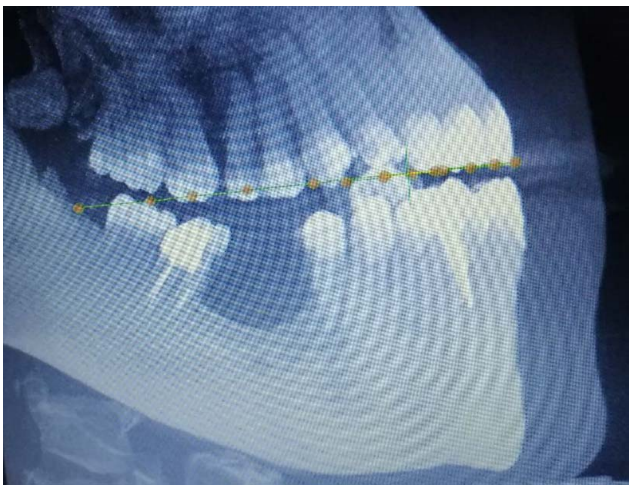

Figure 1. Cone-beam computed tomography scan in panoramic view showing the osteonecrosis in the mandible and maxilla after treatment, and the emptiness left after molar removal.

and swelling in the right mandibular angle and gingivitis. Previously, at the age of 18, he experienced polydipsia, polyuria (6 l per day), weight loss, and low blood pressure (95/50 mmHg). Initial examinations yielded inconclusive results; urine monitoring/output compared with water intake showed equivalent results and normal electrolyte levels (Na: 142.1 mmol/l, K: 4.58 mmol/l). A pituitary resonator (MRI) with gadolinium infusion revealed peduncle thickening without erosion to the Sella turcica, which was diagnosed as a granuloma. A water deprivation test provided no medical evidence, leading to a diagnosis of psychiatric AVP deficiency. The patient was referred to psychotherapy sessions without a favorable response along with desmopressin treatment.

Four years later, he returned to the dental clinic with the aforementioned symptoms. The dentist extracted a molar and conducted a jaw biopsy, the biopsy revealed an inflammatory infiltrate containing both eosinophils and grooved plasma cells consistent with Eosinophilic HX. But mutation tests were not available. Dental cone-beam computed tomography was performed after the surgery (Figs 1, 2). The patient was transferred to the hospital for reevaluation, where additional tests (Table 1) and a bone scan (Fig. 3) were performed. A daily prescription of desmopressin acetate (5.1 mg) and prednisolone (60 mg) was administered for 2 months. However, the improvement was limited to polyuria curing with further mandibular lesion deterioration. Subsequently, he was referred to a multidisciplinary medical committee, including an oncologist, hematologist, orthognathic surgeon, and neurological surgeon, for chemical therapy and jaw surgical repair. The patient is currently undergoing regular chemo sessions with cyclophosphamide (total six sessions, 1 g every 14 days), maintaining a steady state of polyuria treated with desmopressin with no further bone lesions.

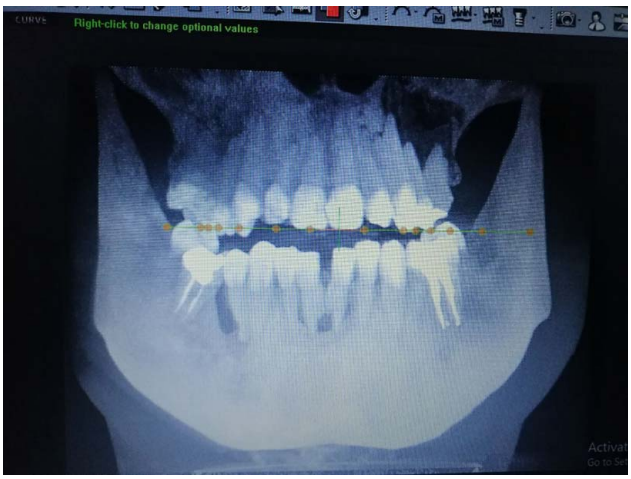

Figure 2. Cone-beam computed tomography scan in panoramic view showing the osteonecrosis in the mandible and maxilla after treatment, and the emptiness left after molar removal.

Discussion and literature review

LCH represents a rare clonal proliferation of Langerhans cells, exhibiting a diverse array of clinical presentations. It has the

Table 1

Examination profiles of the patient.

Clinical examination			
Respiratory system	Dry cough		
Digestive system	Diarrhea alternate with constipation		
Urinary system	polydipsia, polyuria		
Musculoskeletal System	Arthralgia		
General examination	Fatigue, malaise, dizziness		
Laboratory tests			
CBCT			
WBCs	6590	Normal range	4230–9070 C/μl
RBCs	4.60		4.63–6.08 C/μl
Platelets	262		163–337 C/μl
ESR	25		Up to 15 mm/h
Creatinine	57.7 umol/l		45–120 μmol/l
Calcium	2.5 mmol/l		2.15–2.55 mmol/l
Alp	102 U/l		39–140 U/l
Phosphorus	1 mmol/l		0.8–1.6 mmol/l
Potassium	4.75 mmol/l		3.5–5.2 mmol/l
Albumin	48.4 g/l		35–50 g/l
Prolactine_Mindray	11.09 ng/l		Less than 20 ng/l
Urine density	1.015		1.005–1.030
Deprivation test	Polyuria continued (8 l per 8 h) and decreased dramatically after giving desmopressin		
Tissue cassette			
CD1A	Positive		
CD68	POS		
CD20	FEW		
CD03	FEW		
Radiology			
Pituitary resonator MRI	Absence of hypothalamic neurolobe and a nodular lesion in the peduncle measuring 6 mm		
Computerized tomography scan	• Hypoplasia of the frontal follicle, lytic lesion in the right part of the mandible. • Bilateral nodular densities on the upper lobes of pulmonary parenchyma		
Dental Cone-beam Computed Tomography (CBCT)	• Osteonecrosis in the mandible and maxilla		
Bone-scan	• multifocal bone lesions (right tibial bone, mandible, and left 12th rib).		

ALP, alkaline phosphatase; CBC, complete blood count; ESR, erythrocyte sedimentation rate; RBC, red blood cells; WBCs, white blood cells.

capability to impact multiple organ systems, leading to a wide spectrum of clinical manifestations. Its pathogenesis is not completely understood so far, but two primary overarching theories exist regarding its pathogenesis, one suggests that it results from an inappropriate immune response, while the other posits it as a neoplastic disorder[7]. It can be associated with BRAF V600E mutation, MAP2K1 mutation, or activation of MAPK/ERK[1,8]. Among adult individuals, predominant initial symptoms encompass local pain (34% incidence), weight loss (11% incidence), and fever (10% incidence). In addition, patients may exhibit polyuria and polydipsia due to the involvement of the pituitary gland, subsequently resulting in AVP deficiency, and anterior pituitary dysfunction (APD)[3]. Through a systematic search and rigorous selection process, we searched PubMed for similar cases using the following key terms: 'Histiocytosis', 'Pituitary + Bone involvement', and 'diabetes Insipidus' thus the table includes a diverse range of nine cases during the last 10 years (Table 2) that had pituitary disorders as the first noted abnormality; the sex ratio (M:F) above was 1.5:1, although medical literature recorded that the ratio is 2:1[8]. Previous research indicates that the most commonly affected organs in LCH are bone, observed in ~80% of patients, followed by the skin at 33% and the pituitary gland at 25%. Less frequently involved organs include the liver (15%), lung (15%), lymph nodes (5–20%), and the central nervous system apart from the pituitary (2–4%)[1]. The skull and thoracic wall exhibit the highest prevalence of bone involvement in individuals of all age groups, including adults and children. Among children, the spinal column and long bones are the subsequent skeletal sites most frequently affected, whereas, in adults, the spinal column and mandible are the second most commonly affected areas[15]. LCH can be classified into two distinct categories based on its extent of involvement: single-system disease and multisystem disease. Multisystem disease, in turn, can be further subdivided into high-risk and low-risk groups based on the inclusion or exclusion of risk organs such as the hematopoietic system, lungs, liver, and spleen[16]. The literature review table presented above provides a comprehensive overview of relevant cases conducted in the field of LCH. Roughly 70% of MRI findings revealed thickening of the pituitary stalk. AVP deficiency is considered a characteristic indication of a pituitary disorder in LCH. In the first eight patients followed up, AVP deficiency was consistently the first hormonal deficiency observed and the last one presented with a primary infertility[13]. In one patient, AVP deficiency remained the sole endocrine abnormality[2], whereas the majority of patients eventually developed at least one deficiency in an anterior pituitary hormone[1,8,11,14]. Similar findings have been reported in a series of seven cases in which, APD predominantly coexisted with AVP deficiency[17]. In this article, we present a rare case of a hypothalamic-hypophysial axis involved in a male adult who developed central AVP deficiency and a tumor in the jaw bone. Bone involvement in LCH is more frequently observed in children than in adults[16,18]. One of the distinctive aspects of our patient's case is the presence of both pituitary and bone involvement. Various clinical factors also contribute to the difficulty in diagnosing hypothalamic-pituitary region LCH (HPR-LCH). One such factor is lesion depth[19,20]. The clinical features of HPR-LCH are highly similar to those of other HPR diseases, and the symptoms tend to progress and become irreversible. Accurate and timely pathological diagnosis is crucial for HPR-LCH. The typical

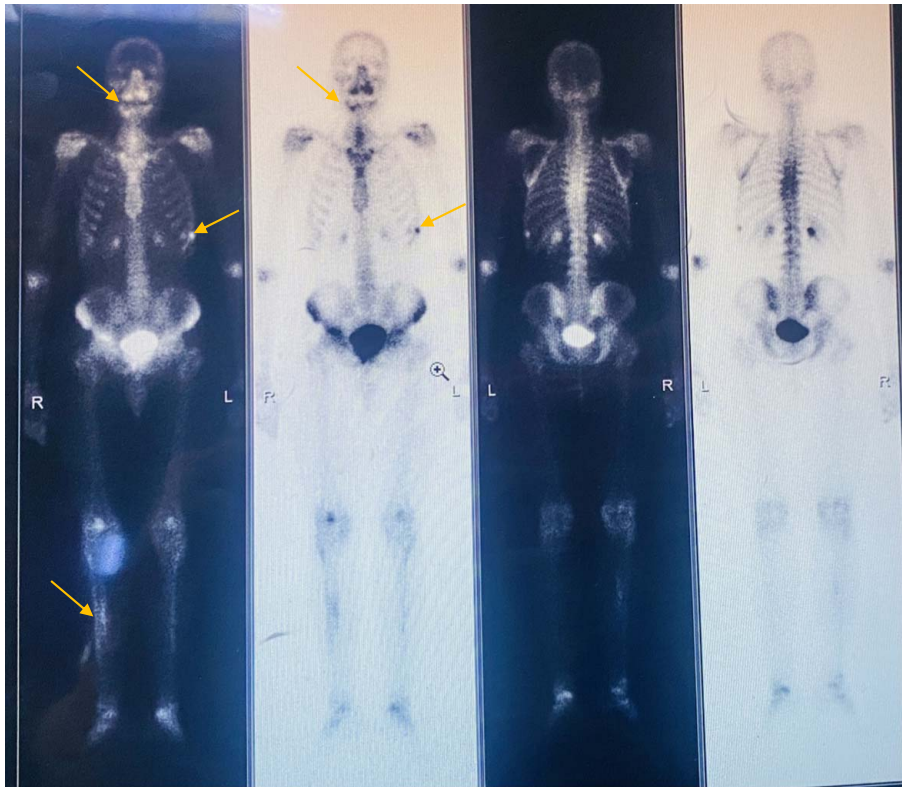

Figure 3. Bone-scan showing multifocal bone lesions (right tibial bone, mandible, and left 12th rib).

Table 2

Summary of nine relevant cases conducted in the field of LCH During the last 10 years, which had DI as the first noted abnormality.

Serial No	Author	Age (years)	Sex	Clinical finding	Treatment	Radiological finding	Systemic characteristics
Case 01	Chen X *et al.* (2012)[9]	14	M	diabetes insipidus and (2) isolated thymic nodules of unknown etiology	Desmopressin then thymectomy	MRI of the head revealed thickening of the pituitary stalk, in addition to loss of high signal intensity of the posterior pituitary lobe	No
Case 02	Ma J *et al.* (2014)[10]	45	M	Hepatitis Symptoms, (DI)	the therapy of prednisolone/desmopressin/vincristine for 12-week followed by maintenance therapy of prednisolone/vinblastine/6-MP	Head MRI revealed an abnormal skull shape with a thickened and large pituitary stalk >3 mm	Yes
Case 03	Ghafoori S *et al.* (2015)[11]	16	F	anterior pituitary dysfunction, (DI)	chemotherapy with prednisolone and vinblastin in 28-day intervals followed by one cycle of radiation therapy	MildI thickening of the pituitary stalk with posterior displacement ($15\times15\times9$ mm)	No
Case 04	Lian C *et al.* (2016)[8]	31	M	anterior pituitary dysfunction, (DI)	regimen of CHOPE (cytoxan, adriamycin, vincristine, prednisone and etoposide) along with oral isotretinoin and the operation of 'debridement, free skin transplantation and thigh skin graft operation'	Cerebrospinal fluid signal in the pituitary fossa	Yes
Case 05	Radojkovic D *et al.* (2018)[12]	31	F	Nonendocrine hypothalamic dysfunction anterior pituitary dysfunction	Surgery then radiation therapy after the reoccurrence	Close to optic chiasm with pituitary stalk encasement ($15\times15\times13$ mm)	No
Case 06	Tan H *et al.* (2019)[1]	49	F	DI, elevated PRL	Surgery and chemotherapy	Enhanced head computed tomography (CT) showed lesions (1.6 1.3 cm) in the sella region. MRI of sella region showed enhanced nodular shadow (about 1.4 cm) on the left hypothalamus	No
Case 07	E Ryan J *et al.* (2020)[3]	49	M	Pneumonia, osteolytic lesions	Etoposide 150 mg/m2 per day for 3 days, at monthly intervals, together with radiotherapy to the T9 vertebral lesion	MRI of the neck and head showed a diffusely bulky pituitary gland with a small focus of low signal within the anterior and inferior aspect of the midline of the adenohypophysis measuring 4 mm and absent posterior pituitary bright spot	Yes
Case 08	Kumar C *et al.* (2021)[13]	25	M	Infertility (decreased levels of gonadotropin hormones). Prolactin levels were high. mild symptoms related to hypothyroidism	Prednisolone and vinblastine (6 weeks with daily 40 mg/m^2 oral prednisolone, and 6 mg/m^2 i.v. vinblastine every 7 days)	MRI of sella revealed a $12.2\times10.4\times8.0$ mm sized intense homogenously enhancing nodular soft tissue mass lesion in the median eminence and the root of infundibulum with thinning of the pituitary stalk. Both lobes of thyroid also had metabolically active nodular lesions on PET – CT	Yes
Case 09	Feng X *et al.* (2022)[14]	26	F	DI (diabetes insipidus) elevated prolactin (PRL). the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estrogen (E2), progesterone (P), and testosterone (T) were below what is normal for adult women	Chemotherapy (vinblastine 4 mg day1, cyclophosphamide 600 mg day1, prednisone 10 mg days1–5) and hormone replacement therapy and antidepressant therapy	The posterior pituitary hyperintensity displayed local enhancement that was lower than the anterior lobe and the pituitary stalk was thickened	Yes

DI, diabetes insipidus; PRL, prolactin.

findings in the biopsy are the presence of Birbeck granules using electron microscopy or positive immunohistochemical staining for the protein markers S100 and CD1a, or by the evidence of transformation and proliferation of Langerhans cells, specifically a pale eosinophilic cytoplasm, irregular and elongated nuclei with prominent nuclear grooves and folds, fine chromatin, and indistinct nucleoli[6]. However, the biopsy procedure and correct diagnosis of HPR-LCH can be quite challenging due to the deep location of the affected tissues, difficulty in obtaining a representative tissue sample, small biopsy specimen size, and reduced inflammatory activity in the specimen following steroid treatment[6]. One limitation of our case is the absence of a comprehensive diagnostic evaluation of all affected areas, including genetic mutation studies. Therapy for patients with LCH remains debatable. As the pathogenesis is not yet clear, various hypotheses lead to diversity in therapeutic approaches. Treatment methods might be a single agent or multimodality therapy including prednisone, topotecan, vinblastine, vincristine, cytarabine, cladribine, or clofarabine[3]. An optimal management is established based on every patient's unique characteristics, for example, whether it is multisystemic or single-system and if the lesion is symptomatic yet[7]. In our case, the patient was given daily desmopressin acetate (5.1) mg and prednisolone (60) mg for 2 months, as prednisolone is recognized for its antitumor properties. before being transferred to cyclophosphamide (Endoxan) since he has a multisystemic LCH with risky system CN involved, so chemotherapy is recommended. Currently, the patient perspective toward his condition has changed as it turned out to be manageable with the appropriate treatments away from the complications of wrong diagnosis, and most importantly with no further bone lesions.

Conclusion

Despite its low incidence, LCH should be considered as a differential diagnosis in patients with AVP deficiency (diabetes insipidus) and ensure an accurate investigation, in addition to interdisciplinary collaboration among healthcare professionals to avoid misdiagnosis, low life quality, and irreversible effects associated with wrong treatments. Furthermore, this case highlights the importance of biopsy results in LCH diagnosis, as it provides direct evidence by examining affected tissue aiding in confirming the diagnosis and rolling out other conditions.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series. We have the approval from the patient to write the case if you want we can send it as e-mail.

Consent

Written informed consent was obtained from the patient's parents 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.

Sources of funding

This research did not receive any grant from funding agencies in the references public, commercial, or not-for-profit sectors.

Author contribution

H.A.: the first author, contributed to drafting editing, reviewing, and bibliography; Y.A.: contributed to drafting, editing, reviewing, data collecting, and corresponding; H.K.: contributed to drafting, editing, reviewing, and data collecting; M.A.: contributed to editing and reviewing; Prof. M.S.: the supervisor, contributed to treating the patient and reviewing. All authors contributed to the final approval for the version to be submitted.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

I confirm that our article is a case report and does not involve a research study requiring registration in a publicable accessible database.

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Data availability statement

Data sharing is not applicable to this article.

Provenance and peer review

The paper is 'Not commissioned, externally peer-reviewed'.

Acknowledgements

The authors wish to show our appreciation to Albairouni University Hospital of Damascus University for their acceptance of students to meet patients and achieve research and Stemosis for Scientific Research, a Syrian Scientific Research official team managed by Dr Nafiza Martini for the scientific environment they provide.

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