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REVIEW ARTICLE

Langerhans cell histiocytosis with spinal, pulmonary and pituitary involvement: What about ACTH deficiency without diabetes insipidus? A propos of a case

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Summary

Langerhans cell histiocytosis (LCH) is disease process characterized by clonal proliferation of CD1a⁺ dendritic cells within an inflammatory infiltrate of hematopoietic derived cells. LCH can manifest with a broad spectrum of symptoms and can involve single organs or have a multisystem distribution. Central nervous system (CNS) involvement of LCH can manifest as granulomatous parenchymal or pituitary mass lesions. Focal, space-occupying lesions, such as masses in the meninges, choroid plexus, and brain parenchyma may contain CD1a⁺ LCH cells, lymphocytes, and macrophages with histology similar to that of extracranial lesions. Here, we describe a rare case of multisystem LCH in an adult patient presenting with spinal lesions and isolated adrenocorticotropic (ACTH) deficiency without diabetes insipidus (DI). In addition, we review the literature summarizing the few reports of hypopituitarism in LCH in the absence of DI.

Key words: *Langerhans cell histiocytosis; brain MRI; anterior pituitary dysfunction; diabetes insipidus*

Introduction

Langerhans cell histiocytosis (LCH) is a rare clonal proliferation with a broad spectrum of clinical manifestations ranging from single organ to systemic involvement with potential life-threatening evolution. LCH is characterised by formation of lesions comprised of neoplastic CD1a⁺ histiocytes and an inflammatory infiltrate of hematopoietic cells, including T-cells, macrophages, and eosinophils [1,2]. It is predominantly a disease of childhood and is rare in adults with a predicted incidence of 1-2 cases per million [3]. LCH of the central nervous system (CNS) typically involves the pituitary gland with patients developing anterior pituitary dysfunction (APD) associated with diabetes insipidus (DI), growth hormone deficiency, and thyroid function abnormalities [4]. Here, we describe a rare case of multisystem LCH in an adult patient presenting with spinal lesions and isolated adrenocorticotropic (ACTH) deficiency without DI, adding to the few reports (3 cases in the English literature) of hypopituitarism in LCH without DI. This case highlights the importance of screening for hormonal deficiencies in patients with LCH and suspected pituitary involvement.

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Case presentation

A 49-year-old patient with a 25 pack year smoking history and no significant medical comorbidities was referred to the urology department for investigation of bilateral flank pain and microscopic haematuria. He underwent flexible cystoscopy, which showed no significant abnormality. A computed tomography (CT) scan of his kidneys, ureters and bladder (KUB) showed no evidence of stones but did reveal several osteolytic areas within the vertebral bodies at the level of T9 and L2 (Figure 1a). It was suggested that these lesions could represent Schmorl's nodes and comparison with previous imaging was recommended. The patient was discharged and later referred for further investigation of the osteolytic lesions.

His only previous admission to hospital had been approximately two and half years before this admission when he presented with a one week history of breathlessness, pleuritic chest pain and right sided loin to groin pain. A CT KUB showed a right sided pneumonia with associated pleural effusion. There was no evidence of destructive osseous lesions at this time. The patient gained symptomatic relief following drainage of the effusion and was treated with antibiotics before being discharged once the pneumonia had resolved.

At re-presentation, he described a 6 month history of worsening pain in his abdomen radiating into his back and constipation for the past 2 months. Although his pneumonia had fully resolved, since that admission he had developed chronic non-progressive back and loin pain which he managed with paracetamol. He was otherwise healthy and reported no history of weight loss, fever, night sweats, trauma or neurological deficit. Full blood count, electrolytes, liver function, renal function, C-reactive protein, serum protein electrophoresis and immunoglobulin levels were within normal ranges.

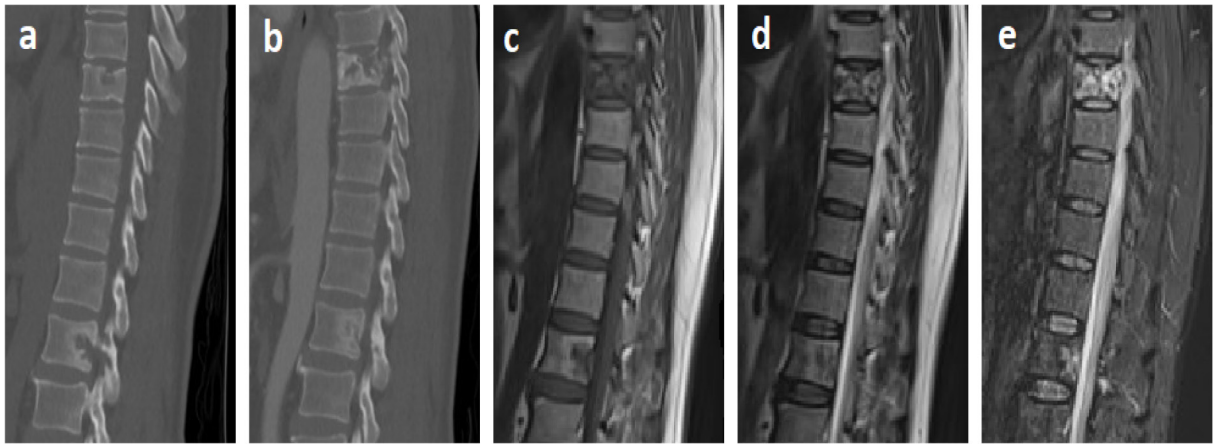

Figure 1. Computed tomography showing osteolytic lesions of the T9 and L2 vertebral body at initial detection **(a)** and four months later on staging scan **(b)** showing further progression of T9 lesion and sclerosis of L2 lesion. Sagittal magnetic resonance images showing focal areas of abnormal signal at the T9 and L2 vertebral body demonstrated on T1-weighted **(c)**, T2-weighted **(d)** and T2-weighted STIR **(e)** imaging.

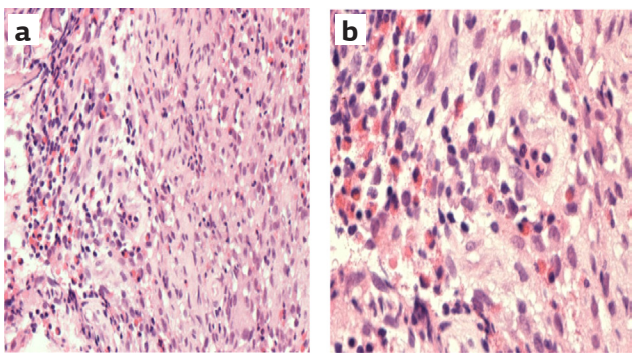

Figure 2. High power magnification image with a mixed population of Langerhans cells with eosinophils and a few lymphocytes **(a)**. Langerhans cells show slightly twisted and indented, sometime reniform nuclei **(b)**.

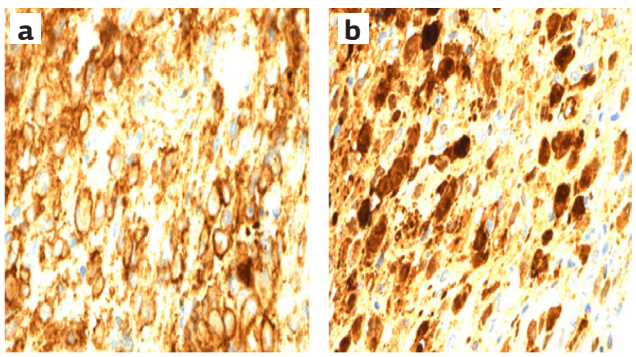

Figure 3. Immunohistochemistry images demonstrate extensive positivity for CD1a [cytoplasmic] **(a)** and S100 [nuclear] **(b)** using an immunoperoxidase staining technique.

A CT chest, abdomen and pelvis (CAP) showed progression of the osteolytic lesion within the T9 vertebral body and further sclerosis of the lesion within the L2 vertebral body occurring during the 4 months since the previous CT (Figure 1b). Several tiny lung nodules were also noted in the right upper and middle lobe. Magnetic resonance imaging (MRI) of the spine revealed loss of height of the T9 vertebral body with abnormal signal intensity extending posteriorly into the pedicles bilaterally as well as abnormal signal intensity in the L2 vertebral body extending into the left pedicle (Figures 1c,d,e). 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. No significant cervical soft tissue or bony abnormalities were identified.

After these initial investigations, the nature of these osteolytic lesions was still not clear and our differential diagnosis included tuberculosis and sarcoidosis, due to the coexisting presence of pulmonary nodules, in addition to typical differentials for osteolytic lesions of the spine such as metastases from an unknown primary and plasma cell myeloma. To help establish a diagnosis, a biopsy was taken from the spine at the T9 vertebra. Histopathologic examination of the sample showed hypercellular fibrotic bone marrow containing sheets of cells with pale round to oval nuclei and copious eosinophilic cytoplasm with histiocytic appearance as well as numerous eosinophils and a few small lymphocytes (Figure 2). Immunohistochemically, the histiocytic appearing cells were strongly positive for S-100 and CD1a (Figure 3). There were also scattered CD3 and CD20 positive T and B lymphocytes and some CD68 positive macrophages. A bone marrow trephine biopsy was also performed which showed normal marrow.

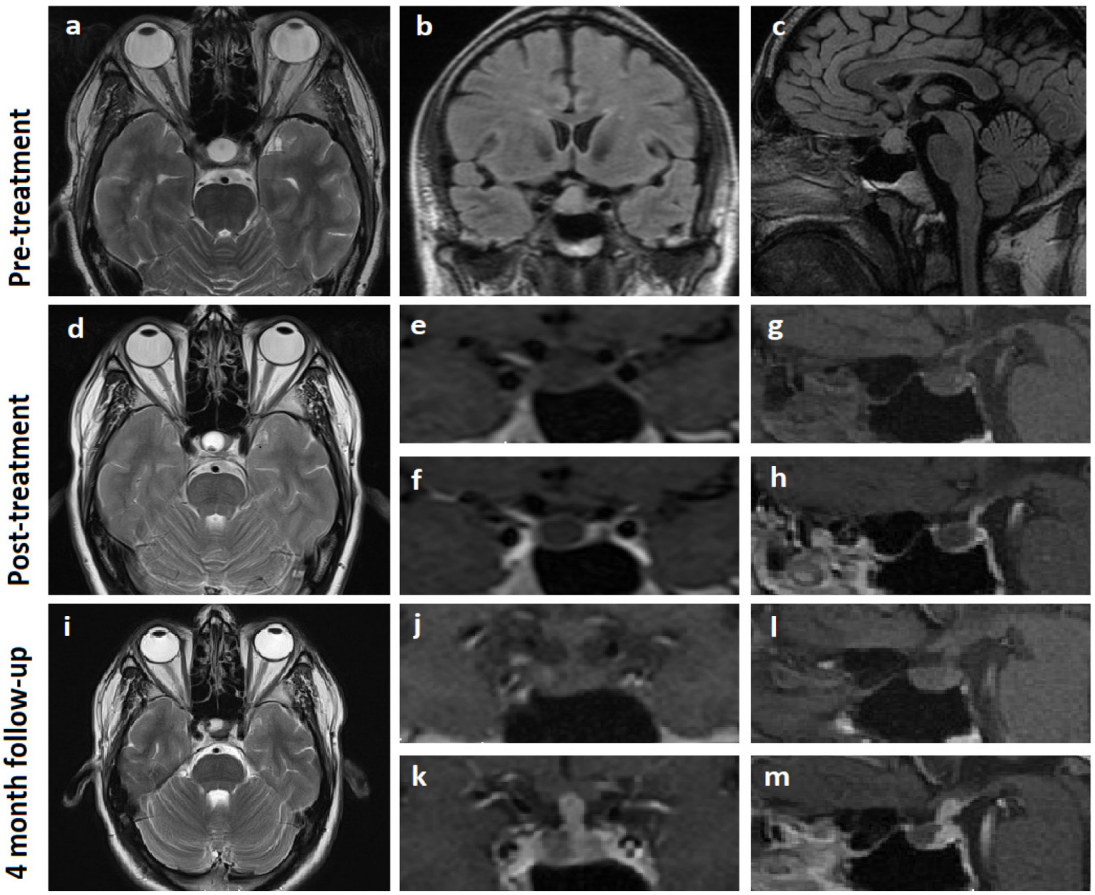

Figure 4. Magnetic resonance imaging (MRI) of brain at presentation with headache and nausea on T2-weighted axial **(a)**, coronal **(b)** and T1-weighted sagittal **(c)** slices showing a bulky anterior lobe of the pituitary gland with absent posterior pituitary bright spot and displacement of the pituitary and pituitary stalk. Post treatment MRI of brain on T2- weighted axial **(d)**, T1-weighted pre and post gadolinium contrast coronal **(e,f)** and sagittal **(g,h)** slices showing a mostly cystic appearing nodule with interval reduction in size. 3 month follow-up MRI of brain on T2- weighted axial **(i)**, T1-weighted pre and post gadolinium contrast coronal **(j,k)** and sagittal **(l,m)** slices showing further reduction in size of the cystic nodule involving the anterior lobe of the pituitary gland and new evidence of marked thickening of the pituitary stalk and infundibulum with avid post contrast enhancement.

The clinical picture and the biopsy findings were consistent with a diagnosis of multi-system LCH with spinal and pulmonary involvement. After confirmation of the disease, [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography (PET) was performed which showed increased FDG uptake at the T9 vertebra with a maximum standard uptake value (SUV) of 8.5. Increased FDG activity was also seen in the sacrum adjacent to the left sacral-iliac joint likely representing a further focus of disease. There were also scattered foci of low intensity FDG activity in the upper lobes of both lungs, reflecting active pulmonary involvement. Mixed lytic and sclerotic areas were identified at the L2 and L5 vertebra but these were non FDG avid and were thought to represent inactive (healed) disease.

Several months after initial diagnosis, the patient presented to hospital with a one week history of severe headache and vomiting. He reported no polyuria or polydipsia; biochemistry revealed severe hyponatraemia (Na^+: 113 mEq/L), and a serum cortisol level of 49 nmol/L. Even though ACTH had not been evaluated at that point, it was felt that this was likely hypocortisolism, secondary to pituitary involvement and a repeat MRI of his pituitary was performed which showed a sellar mass displacing the pituitary gland with no significant change in volume compared to previous imaging and absent posterior pituitary bright spot (Figures 4a, b, c). Based on that, the patient was treated with hydrocortisone substitution.

The patient was subsequently treated with etoposide 150 mg/m^2 per day for 3 days, at monthly intervals, in addition to radiotherapy to the T9 vertebral lesion. Post treatment PET scan showed stable pulmonary disease with no residual metabolic activity at the T9 vertebra. However, there was progression noted in the L2 lesion with new FDG uptake (SUV 5.9) not present on the previous study and new metabolically active lesions were identified in the left iliac bone (SUV 4.8) and left inguinal node. A small FDG avid nodule was also noted within the pituitary gland. Post treatment contrast MRI showed interval reduction in the previously identified soft tissue nodule involving the anterior lobe of the pituitary with a mostly cystic appearance and regression of suprasellar extension (Figure 4). Four month follow-up MRI showed further reduction in size of the cystic nodule but new evidence of marked thickening of the pituitary stalk and infundibulum with avid post contrast enhancement (Figure 4). The patient remains clinically stable without headache, cognitive deficits and/or changes in memory and concentration and has returned to his work and normal daily activities.

Discussion and literature review

LCH is a rare clonal proliferation of Langerhans cells with a broad spectrum of clinical manifestations. It can affect several organ systems and as such has a wide range of clinical manifestations. In adult patients, local pain (34%), weight loss (11%) and fever (10%) are the most common presenting complaints. Patients can also present with polyuria and polydipsia due to pituitary gland involvement and subsequent DI as well as APD. Other symptoms include skin rash, lymphadenopathy, gingival hypertrophy, neurological deficit as well as cough, dyspnoea and chest pain depending on the organ system involved. LCH can be categorised into single-system and multisystem disease, with multisystem disease further stratified into high-risk and low-risk groups depending on whether risk organs, including the haematopoietic system, lungs, liver and spleen, are involved or not [5]. In adults, multisystem disease accounts for approximately two-thirds of cases with bone, lung, skin, pituitary, spleen/liver and thyroid involved in decreasing order of frequency. Pulmonary disease is most often seen in patients with single-system LCH followed by bone involvement [6]. Due to the wide range of clinical presentations, LCH can present a diagnostic challenge and conclusive diagnosis of LCH is normally achieved by histologic and immunophenotypic examination of a biopsy taken from an accessible lesion. The distinguishing histological features are the presence of prominent eosinophilic infiltration with scattered large epithelioid/histiocyte-like cells with convoluted nuclei. Immunohistochemistry reveals cells which stain positive for CD1a, S100-protein and CD68 [7].

Central nervous system is frequently involved by LCH with hypothalamo-pituitary axis localization more frequently observed often leading to DI. Isolated CNS-LCH is rare with few reported cases and CNS involvement typically occurs in the context of multi-system disease with pathogenesis attributed to LCH-infiltration and scaring of the hypothalamic pituitary area or autoimmune process involving antibodies to vasopressin [8]. The prevalence of CNS involvement with DI in adult patients with multi-system disease is 30% and, once established, DI is often permanent requiring lifelong hormone replacement [6,9,10]. APD is seen in up to 20% of patients with LCH and is almost invariably associated with DI, often with panhypopituitarism, with very few reported cases of APD without DI [4,11-13]. The first case of isolated APD without DI was reported in 1991 by Tabarin et al, with anterior panhypopituitarism observed in a 53 year-old female with multisystem LCH with

Table 1. Cases of Langerhans cell histiocytosis with anterior pituitary dysfunction without diabetes insipidus

Author, Year of publication [Reference]	*Age at diagnosis*	*Sex*	*Classification of disease*	*Presenting complaint*	*MRI brain findings*	*Hormonal abnormalities*
Tabarin A et al, 1991 [14]	53	F	Multisystem	Psychiatric disturbances	Suprasellar mass	↓TSH, ↓ACTH, ↓LH, ↓FSH, ↓GH
Balaguruswamy S et al, 2011 [15]	48	M	Multisystem	Not reported	Empty sella	↓LH, ↓FSH, ↓TSH, ↓GH
Radojkovic D et al, 2018 [16]	31	F	Single system	Amenorrhea, weight gain, oedema, headaches, blurred vision	Suprasellar mass encasing pituitary stalk	↑PL*, ↓ TSH, ↓FSH, ↓LH
Present case	48	M	Multisystem	Back pain	Suprasellar mass	↓ACTH

F: female; TSH: thyroid stimulating hormone; ACTH: adrenocorticotropic hormone; LH: luteinising hormone; FSH: Follicle-stimulating hormone; GH: growth hormone; M: male; PL: prolactin; * Raised prolactin in this case was attributed to encasement of pituitary stalk by suprasellar mass

cutaneous involvement [14]. Twenty years later, Balaguruswamy et al reported a 48 year-old male with multisystem LCH involving the groin, external auditory meatus, scalp, gum, mandibular bone, perineum and axilla. The patient developed partial hypopituitarism 18 years following initial diagnosis with no evidence of DI 4 years after pituitary involvement [15]. Most recently, Radojkovic et al described a case of single system CNS-LCH with partial hypopituitarism without DI in a 31 year-old female with elevated prolactin which they attributed to pituitary stalk encasement resulting in prolactin inhibition due to reduced dopamine release [16]. These cases are summarised in Table 1.

ACTH deficiency is described in 1-2% of patients with LCH typically in multisystem disease determining panhypopituitarism and DI [4]. Due to the potentially life-threatening consequences of ACTH deficiency, it is important to assess basal and dynamic cortisol values when pituitary involvement has been demonstrated, as well as screen for other hormone deficiencies. MRI with gadolinium contrast has proved useful in the evaluation of the pituitary gland in patients with LCH and patients with DI or APD nearly always have abnormal pituitary imaging [4,17]. The most common MRI abnormalities are infundibular thickening and loss of the 'bright spot' of the posterior pituitary on T1-weighted sequences and it has been noted that the radiological abnormalities often predated development of APD [12,17,18].

Therapy for patients with CNS-LCH remains a dilemma. Only a few series with small numbers of patients or case reports have been published so far. LCH has an inflammatory component that contributes to focal tissue injury and the clinical phenotype. The various therapeutic approaches reflect the different pathogenic hypotheses. Tumorous lesions in the hypothalamic pituitary region, the meninges, or choroid plexus are located outside the blood-brain barrier and, therefore, may be accessible for systemic treatment. Parenchymal mass lesions of the brain due to CNS-LCH may respond to either single agents or combined therapeutic strategies consisting of prednisone, topotecan, vinblastine, vincristine, cytarabine, cladribine, or clofarabine [19-22].

In view of the recent advances in the knowledge of molecular biology of LCH, targeted treatment represents an attractive therapeutic approach for CNS-LCH. Indeed, approximately 75% or more of these patients harbor activating BRAF or MEK mutations. As such, vemurafenib, dabrafenib, cobimetinib, and trametinib have activity against LCH and are emerging therapeutic options [23,24].

The efficacy of radiotherapy has not yet been clarified.

Conclusion

We describe a case of multisystem LCH with spinal and CNS involvement with isolated ACTH deficiency without evidence of DI. On initial evaluation, our patient had no symptoms of ACTH deficiency but did have changes on MRI of the brain revealing evidence of CNS involvement with bulky pituitary gland and absent posterior pituitary bright spot. This highlights the role of MRI in the initial assessment of patients with LCH and, the importance of monitoring for pituitary dysfunction in patients with evidence of CNS involvement.

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All authors contributed to the collection, analysis, interpretation of data, and the writing of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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