Neurological Sciences (2019) 40:1055–1058
https://doi.org/10.1007/s10072-019-3709-y

BRIEF COMMUNICATION

Langerhans cell histiocytosis presenting as a rapidly evolving frontotemporal syndrome

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Received: 6 October 2018 / Accepted: 7 January 2019 / Published online: 10 January 2019

Abstract
Langerhans cell histiocytosis (LCH) is a rare disorder in adults which usually manifests with involvement of multiple organ systems, including the central nervous system. We describe an unusual case of biopsy-proven LCH presenting with frontotemporal-dominant cognitive impairment with hypothalamic involvement, along with multisystem disease. We propose that the dementia was probably an immune-mediated process triggered by LCH which responded dramatically to high-dose steroids.

Keywords Langerhans cell histiocytosis · Hypothalamus · Cognition · Dementia

Introduction

Langerhans cell histiocytosis (LCH) is a multi-organ disorder that also affects the central nervous system (CNS). Classically, CNS manifestations in LCH involve the hypothalamus-pituitary system that may present with diabetes insipidus, and uncommonly, neurocognitive issues. We describe a case of histopathology proven LCH in a 35-year-old male patient who presented with fronto-temporal syndrome with hypothalamic, paravertebral and bony lesions on imaging.

Case report

A 35-year-old male presented to our hospital with 13-month history of progressive behavioural problems with a dysexecutive syndrome leading to errors of judgement at work and increasing somnolence and apathy. Around 3 months later, his behaviour became aggressive, with bladder and bowel incontinence. He also developed anorexia and significant weight loss. He was evaluated at another centre where magnetic resonance imaging (MRI) brain revealed a hypothalamic mass. He was empirically given oral dexamethasone for 12 weeks during which his aggression improved slightly. However, he relapsed following steroid discontinuation. He also developed severe neck pain and left lower limb radicular pain.

Examination revealed an emaciated man with normal systemic examination. Mini-mental status examination was 14/30. Lobar evaluation revealed gross derangement of frontal and temporal functions (Table 1). Left knee jerk was absent and ankle reflex was sluggish. The remaining examination including cranial nerves, motor, sensory and cerebellar systems was normal.

His hemogram, peripheral blood film, renal and thyroid functions were normal. Hepatic function test showed elevated alkaline phosphatase. Prolactin was elevated. MRI brain revealed thickening with enhancement of infundibulum and tuber cinerium. Ill-defined T2/FLAIR hyperintensity was seen extending into the adjacent hypothalamus (Fig. 1a). MRI spine showed an enhancing T2 hyperintense lesion in C5 vertebral body with a well-defined lobulated right paravertebral soft tissue component from C4 to C6 level (Fig. 1b). Other enhancing lesions were seen in the D12 vertebral body, left S2 and

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Table 1 Neuropsychological tests before and after treatment

Neuropsychological tests	Score (pre-treatment)	Score (3-month posttreatment)
Mini-Mental State Examination	14/30	21/30
Attention/working memory		
Digit forward span	3	5
Digit backward span	1	3
Language assessment	Normal	Normal
Frontal Assessment Battery	6	12
Temporal lobe assessment		
Recent memory	Impaired	Improved
New learning ability	0/5 objects recalled	3/5 objects recalled
Parietal lobe assessment		
Visuospatial orientation	Normal	Normal
Occipital lobe assessment		
Visual agnosia testing	Normal	Normal
Prosopagnosia testing	Normal	Normal

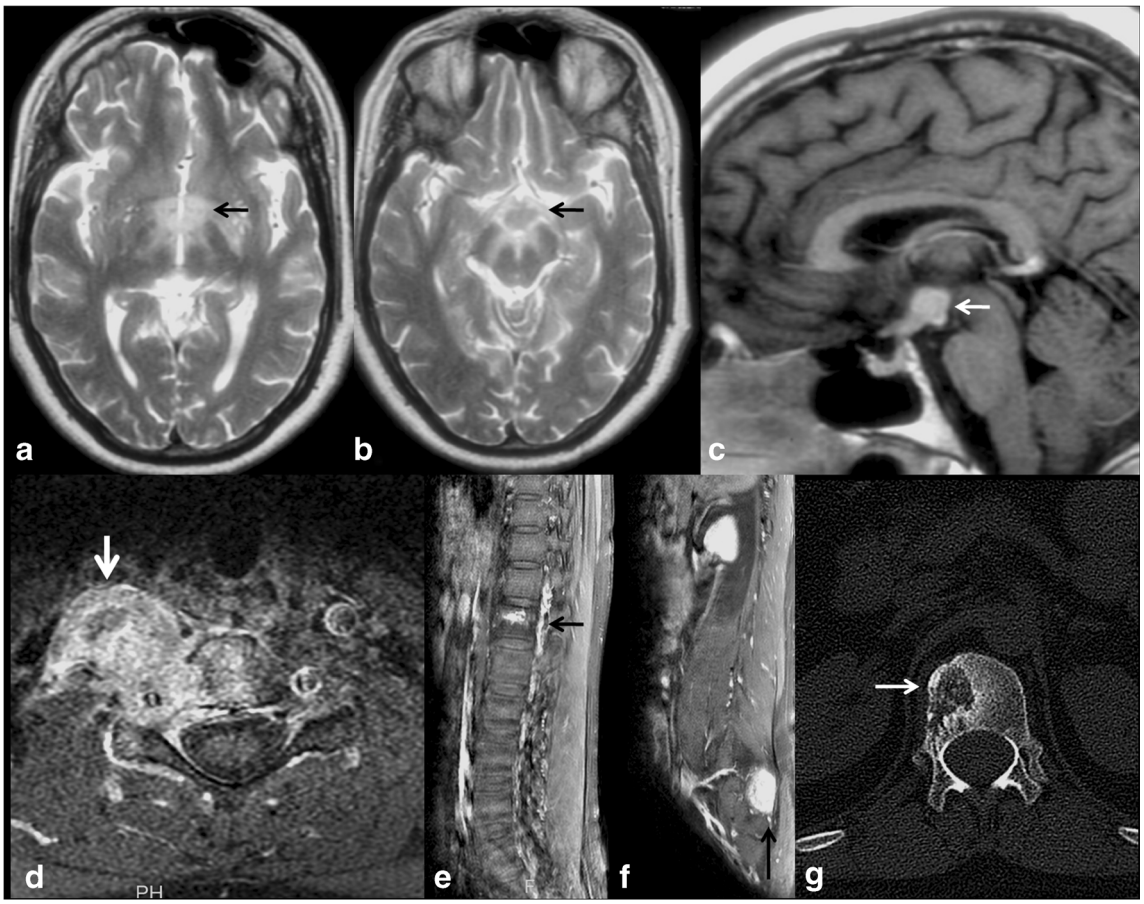

Fig. 1 A 35-year-old male patient with history of progressive behavioural problems. Axial T2 (**a**, **b**), sagittal post contrast T1(**c**)-weighted images show thickening with enhancement of the infundibulum and tuber cinerium (arrow in **b**, **c**) and ill-defined T2/FLAIR hyperintensity extending into the adjacent hypothalamus (arrow in **a**). Post contrast T1-weighted axial image (**d**) shows an enhancing lesion involving the body of C5 vertebrae with an associated large soft tissue component seen in right paravertebral region extending from C3 to C6 vertebra level, without epidural/intradural extension. Sagittal post contrast T1-weighted images (**e**, **f**) show enhancing lesions in D12 vertebral body (arrow in **e**) and the right iliac bone (arrow in **f**). Axial NCCT (**g**) at D12 level reveals a lytic lesion with minimal surrounding sclerosis

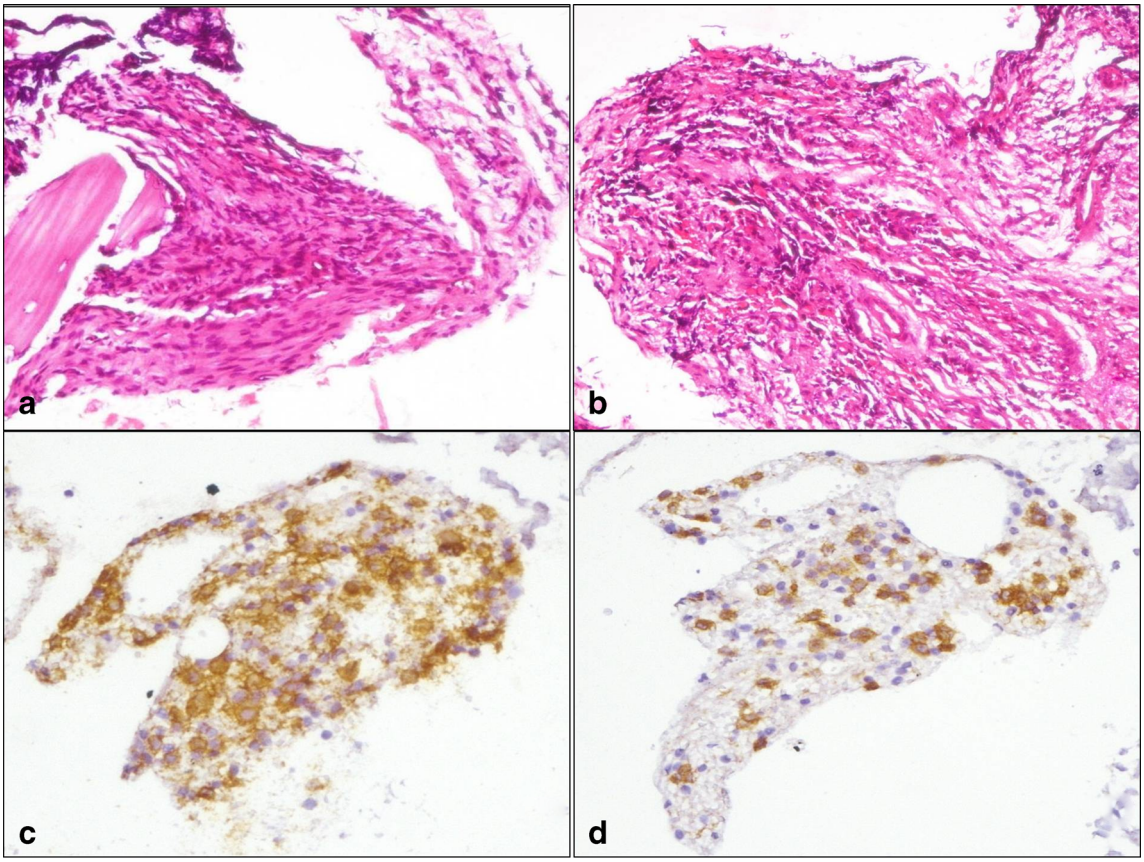

Fig. 2 Biopsy from sacral soft tissue mass. Photomicrographs show bony tissue fragments with chronic inflammatory infiltrate and marked crush artefact. Few atypical cells with moderate eosinophilic cytoplasm and ovoid nuclei are present (**a**, **b**: HE, × 20). Immunohistochemistry shows positivity for CD1a (**c**: IHC, × 20) and langerin (**d**: IHC, × 20)

right iliac bone. Whole body FDG-PET showed elevated metabolic activity in the right cervical paravertebral soft tissue mass, periportal and pericaval lymph nodes with multiple skeletal lesions. Cerebrospinal fluid was clear with no cells, normal sugar (55 mg%) and protein (42 mg%) with no evidence of any infection or malignancy. Serum protein electrophoresis was normal. Abdominal ultrasonography showed mild hepatosplenomegaly. Fine needle aspiration cytology from the paravertebral soft tissue mass showed acute inflammatory exudate without any granulomas or acid-fast bacilli. During admission, he developed sudden hypotension which was managed with intravenous steroids as well as inotropic support. CT-guided biopsy of the right iliac bony lesion was performed. This (Fig. 2) was suggestive of LCH. He was initiated on high-dose intravenous dexamethasone to which he responded dramatically with resolution of hypotension and return of normal appetite. He was transferred to oncology services where he was started on high-risk protocol chemotherapy with prednisolone (40 mg/m^2) and vinblastine (6 mg/m^2 weekly) for 6 weeks. Subsequently, 6-mercaptopurine (50 mg/m^2) was added along with vinblastine and prednisolone. At 3 months of follow-up, his lesions had diminished, and his behavioural issues had improved remarkably.

Discussion

Disorders of histiocytosis have been classified as L, C, H, R and M groups [1]. LCH, a rare disorder belonging to the L (Langerhans) group is characterised by proliferation of cells that immunophenotypically and morphologically resemble antigen-presenting Langerhans cells in skin and mucosa [2]. The incidence is 3–5 per million in children and 1–2 per million in adults [3]. The bones are most commonly involved [4]. CNS involvement is found in 12% and in 6% at presentation [5]. In our patient, CNS was affected at presentation with a predominant frontotemporal syndrome. Pituitary infiltration may give rise to central diabetes insipidus (DI) and other endocrinological abnormalities [5]. In our patient, hormonal profile including ACTH, TSH and serum cortisol were normal. Neurodegenerative CNS disease in LCH (ND-LCH) develops several years (3–15 years) after the initial diagnosis, with cerebellar features, psychomotor retardation and

psychosis [6]. However, our patient presented with dementia. One possibility to explain the same may be an immune-mediated dementia triggered in the setting of histiocytosis. Neuropathological studies show the presence of granulomas with predominance of CD8 T-cells [7]. This could also explain why the patient responded dramatically to steroids. Immune-mediated dementias have been described well in association with myriad antibodies including anti-NMDA, ant-VGKC and anti-AMPA receptor antibodies. However, there has been no case report thus far in literature to describe a similar phenomenon or antibody related to LCH. The other possibility could be the hypothalamic lesion itself or by a disconnection syndrome as the hypothalamus is well connected to anterior limbic structures. A case report describes hypothalamic amnesia and frontal lobe dysfunction with LCH [8]. A recent report describes hypothalamic, pituitary and even basal ganglia and brain parenchymal enhancing lesions in a case of CNS LCH presenting with endocrinological disturbances [9]. Our patient developed refractory hypotension not responsive to fluids and medium-dose intravenous steroids. Adrenal involvement by the primary disease process was considered a possible cause. However, ACTH stimulation tests could not be performed as the patient required inotropes. Adrenal involvement is extremely rare, described in 0.5% of cases with LCH. The other possibility was autonomic dysfunction due to hypothalamic involvement. Recent guidelines for the treatment of CNS-LCH are based on chemotherapeutic regimens with vinblastine/prednisolone or cytarabine monotherapy along with extensive neuroradiological and clinical monitoring [10].

Conclusion

Hypothalamic lesions due to LCH may present with neurocognitive syndrome. Bony involvement must be sought and used for diagnosis if accessible. Hypotension in LCH may be multifactorial, either due to hypothalamic involvement causing dysautonomia or due to adrenal involvement leading to relative adrenal insufficiency.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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