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Case report

An adult progressive Langerhans cell histiocytosis with central nervous system involvement for 10 years: A case report

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ABSTRACT

Introduction: Langerhans cell histiocytosis (LCH) is a rare disease that usually occurs in children <15 years of age. Adult-onset LCH is extremely rare. Previous published guidelines and studies mainly focused on pediatric patients. The rarity and also insufficient knowledge of LCH in adults, especially central neuvous system (CNS) involvement of LCH, often resulted in missed and delayed diagnosis.

Case presentation: A 35-year-old woman presented with cognitive impairment, anxietydepression, decreased eyesight, skin rash, hypernatremia, gonadal hormone deficiency and hypothyroidism. She had experienced menstrual disturbance and infertility since 10 years ago. MRI examination showed a mass lesion in the hypothalamic-pituitary region. Sighs of radiologic neurodegeneration were not found on brain MRI scans, however. Biopsy of skin rash confirmed the the diagnosis of multisystem LCH. BRAF V600E mutation was detected in the peripheral blood mononuclear cells. She accepted combination chemotherapy of vindesine and prednisone and accquired partial remission. The patient died of severe pneumonia during the second course of chemotherapy.

Conclusion: Given the complicated differential diagnoses of neuroendocrine disorders, it was essential to be aware of CNS involvement of LCH at first, especially in adults. BRAF V600E mutation may participated in disease progression.

1. Introduction

Langerhans cell histiocytosis (LCH) is a neoplasm of pathologic dendritic cells characterized by CD1a and Langerin surface antigens. Almost 60% of LCH cases harbor the BRAF-V600E mutation [1]. Any organ or system of the human body can be affected, but those more frequently involved are the skeleton (80% of cases), the skin (33%), and the pituitary (25%). Other organs involved are the liver, spleen, the hematopoietic system and the lungs (15% each), lymph nodes (5–10%), and the central nervous system excluding the pituitary (2–4%) [2]. Adult-onset LCH is extremely rare, with an estimated incidence of 0.07 cases per million. The median overall survival in the entire cohort of adult disseminated LCH was 255 months [3].

2. Case presentation

A 35-year-old woman presented with memory difficulties and blurred vision. According to her family, the patient had been exhibiting emotional instability, agitation, apathy, anorexia and drowsiness for 5 months and recurrent oral mass for 1 year. Medical history revealed menstrual disturbance (oligomenorrhea or amenorrhea) and infertility since 10 years ago and she was diagnosed with gonadal hormone deficiency 6 years ago. She suffered excessive thirst and polydipsia one year ago and didn't seek medical advice.

On admission, Vital signs were normal, and her body mass index was 14.42 kg/m^2. The patient was drowsy and disorientated. Skin examination noted withered hands and scattered distribution of white papula on scalp and red maculopapule on the trunk. The neurological physical examination was normal except mild kinetic tremor, hyperalgesia and

Abbreviations: CT, Computed tomography; MRI, Magnetic resonance imaging; BRAF, B1 v-raf murine sarcoma viral oncogene homolog; MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; LH, Luteotropic hormone; FSH, Follicle-stimulating hormone; ACTH, Adrenocorticotropic Hormone; TSH, Thyroid stimulating hormone; HIV, Human immunodeficiency virus; PCR, Polymerase Chain Reaction; i.v., intravenous.

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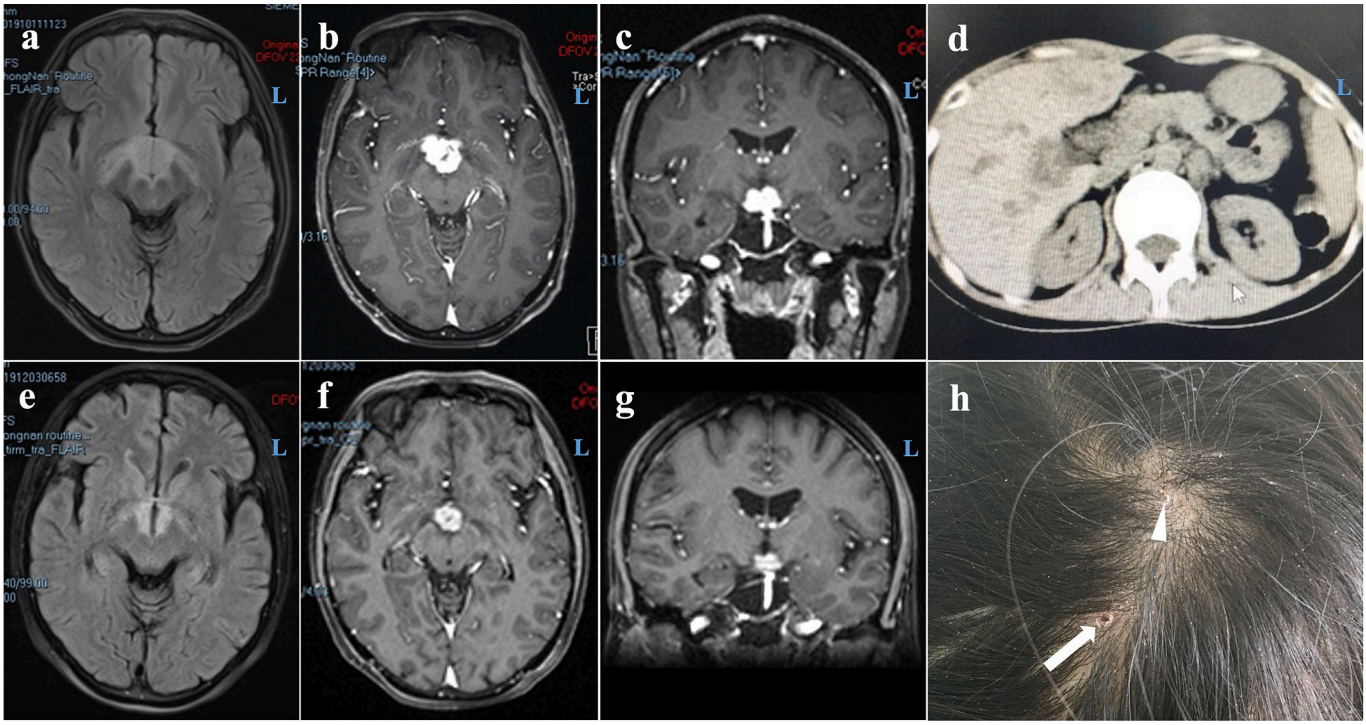

Fig. 1. **(a ~ c)**Brain MRI at baseline showed soft tissue with irregular shape in the sella region, which resulted in mild edema around the lesion **(a)** and homogeneous enhancement **(b, c)**. **(d)** Abdomen CT scan revealed a mass lesion with hypodensity in the hepatoportal region. **(e ~ g)** Post-chemotherapy brain MRI showed alleviation of the hypothalamic mass lesion. "L" indicates left side. **(h)** The patient underwent a biopsy of the scalp rash. Arrow head indicated the rash. Arrow indicated crusted papula after biopsy.

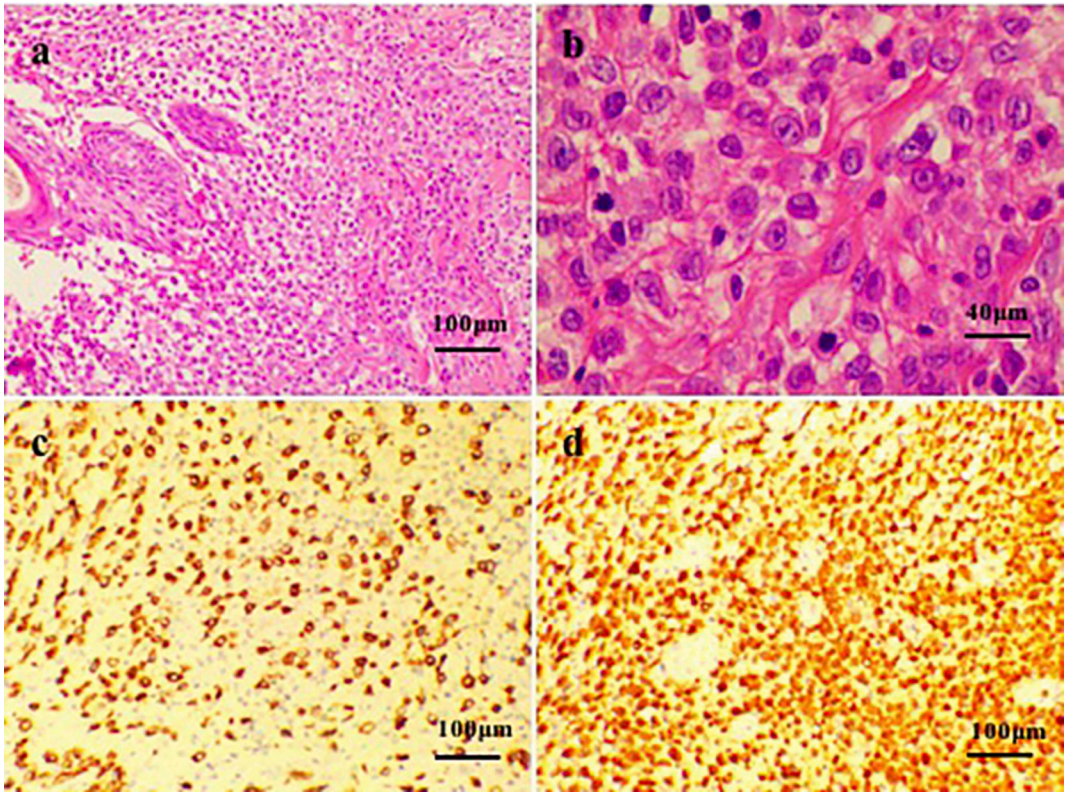

Fig. 2. Histopathological examination from a scalp biopsy. **(a, b)** Hematoxylin and eosin staining (**a**, ×40), (**b**, ×100). **(c, d)** Immunohistochemical examination of histiocytes was positive for CD1a (**c**, ×40) and S-100 (**d**, ×40).

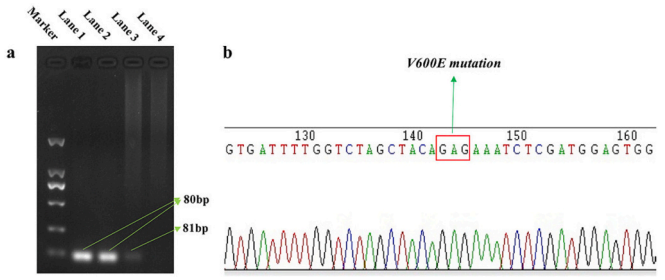

Fig. 3. (a) We performed semi nested PCR to detect the T1799A transversion mutation.
Using the forward primer 5′-GGTGATTTGGTCTAGCTACAG-3′ and the reverse primer 5′-CCACAAAATGGATCCAGACAAC-3′, a short gene fragment of 81 bp was amplified by the first run. The products, which was visualized by gel electrophoresis (lane 3), was amplified a second time with a forward primer 5′-GTGATTTGGTCTAGCTACAGA-3′ (the last nucleotide corresponding to the T1799A transversion mutation) and the same reverse primer, generating a more prominent 80 bp band in the gel (lane 1, 2). Lane 4 was a negative control. **(b)** The 80 bp fragment was further analyzed by sanger sequencing, demonstrating the mutation of T to A transversion at nucleotide position 1799 (codon 600).

week tendon reflexes. Neuropsychological test suggest global cognitive deficits, especially in orientation, memory, visuospatial ability and calculation (MMSE total score 17, MoCA total score 11) and definite anxiety (Hamilton Anxiety Scale score 17) and mild depression (Hamilton Depression Scale score 25).

Blood workup showed normocytic anemia, hypernatremia (161.8 mmol/L) and hyperchloraemia (123.5 mmol/L). She didn't developed diabetes insipidus. Her 24 h urine volume were approximately 1000 mL. Although the urine osmolality was low (72 mOsm/kg), urine specific gravity and 24-h urinary sodium and chloride was normal. She was no responsive to fluid deprivation-vasopressin test. Hormonal measurements showed a dramatic decline in cortisol level (1.39 μg/dL, reference value 8.7–22.4) and all the sexual hormones including progesterone, LH, FSH, prolactin, testosterone and estradiol. The circadian ACTH rhythm was within the normal range. Thyroxine was decreased (free T3 2.58 pg/mL, reference value 1.71–3.71; free T4 0.55 ng/dL, reference value 0.70–1.48) with elevation of TSH (5.21uIU/mL, reference value 0.35–4.94). Growth hormone was at normal range (1.1 ng/mL, reference value 0.10–6.88). ESR was high (81 mm/h, reference value 0–20). Vitamin, autoimmune antibodies, HIV, and syphilis screening was normal.

Electroencephalogram manifested slow wave of 6 hertz in all the recording electrodes. Magnetic resonance imaging (MRI) of the brain demonstrated increased T2 signal with a gadolinium enhancement lesion in the hypothalamic region extending into the suprasellar region (Fig. 1a, b, c). Chest computed tomography (CT), skull CT revealed normal findings. Abdominal CT showed a hypodensity lesion within the liver (Fig. 1d).

Since the hemorrhage risk of obtaining a diagnostic biopsy of the hypothalamus is high according to the neurosurgeon, the patient underwent a biopsy of the scalp rash (Fig. 1h). The pathology showed proliferation of inflammatory cells accompanied by significant mitosis (Fig. 2a, b). The immunohistochemistry of the biopsy specimen showed that the lymphohistiocytic infiltration was positive for CD1a, S100 protein (Fig. 2c, d), Langerin, CD68, CyclinD1, Ki-67 while negative for keratin, CD30−), LCA(−), Lysozyme(−) (data not shown). Thus, the patient was finally diagnosed with multisystem LCH. BRAF V600E mutation were detected in PBMCs through DNA sequencing analysis of PCR amplification products of a fragment of the BRAF gene spanning the nucleotide 1799 T > A mutation hotspot at codon 600 using the specific primers (Fig. 3).

She accepted combined treatment of vindesine 6 mg/m^2 i.v. weekly bolus for 6 weeks, with prednisone 40 mg/m^2/day orally in three divided doses for 4 weeks and then tapered over the following 2 weeks. Oral levothyroxine (25 μg daily) and escitalopram (10 mg daily) were given. After the first 6 weeks of treatment, skin rash gradually dissipated, and the second brain MRI showed regression of the hypothalamic mass lesion but mild brain atrophy (Fig. 1e, f, g). Although anxiety (Hamilton Anxiety Scale score 13) and depression (Hamilton Depression Scale score 21) was alleviated, MMSE test showed no improvement of preexisting cognitive deficits and slightly deterioration of executive function and attention (MMSE total score 15). Electroencephalogram remained slow rhythm of 6 hertz. Hypernatremia was not alleviated, and 24-h urinary sodium and chloride declined dramatically (urinary sodium 108.3 mmol/d, urinary chloride 98.0 mmol/d). Sexual hormones stayed at low level. Free T3 and TSH both decreased compared to the first visit (free T3 1.58 pg/mL, TSH 0.5747uIU/mL). Moreover, growth hormone dropped below normal range (0.05 ng/mL).

Therapeutic schedule with vindesine and steroids for another 6 weeks (vindesine 6 mg/m^2 i.v. weekly bolus, and prednisone 40 mg/m^2/day orally in three divided doses for 3 days every week) was advised. Unfortunately, she was infected by pneumonia and died of respiratory failure during the second course of chemotherapy.

3. Discussion and conclusions

The rarity of LCH in adults, combined with the nonspecific and varied clinical presentations, typically result in missed and delayed diagnosis [4]. Although this patient exhibited neuroendocrinopathies as early as 10 years ago, she didn't undergo any brain imaging examination until she suffered cognitive impairment and psychiatric disturbances. Histopathologic diagnosis of LCH was confirmed for all patients using S-100 and/or CD1a antigen positivity screening [1]. To avoid a CNS biopsy, we performed scalp biopsy, validating the chronicity or reactivation of LCH.

CNS involvement of LCH can be divided in focal mass lesions and lesions associated with progressive neurodegeneration. Neurodegenerative LCH is characterized by “LCH-associated abnormal CNS imaging” (LACI) for the radiologic findings and “LCH-associated abnormal CNS symptoms” (LACS) for patients with abnormal clinical cognitive and psychological findings [5]. It was reported that neurological syndromes associated with LACS seem to correlate poorly with the extent of abnormalities seen on conventional MRI [6,7]. Despite LACS including mild tremors, abnormal reflexes, behavioral changes, cognitive abnormalities and psychiatric problems, signs of radiologic neurodegeneration were not found on MRI scans in our patient, raising the possibility for a paraneoplastic etiology, inflammatory, and/or neoplastic pathogenic mechanisms for LACS [8].

The discovery of BRAF-V600E mutation in peripheral blood mononuclear cells provided possible evidence that LCH in our patient could arise from a mutated hematopoietic precursor and the underlying pathogenic mechanisms of neurodegeneration may be driven by a neoplastic process of hematopoietic origin [9]. Studies have reported that BRAF V600E mutation was associated with organ involvement that could lead to permanent, irreversible damage, such as neurologic and pituitary injuries. Compared with patients with wild-type BRAF, patients with BRAF V600E mutation more commonly displayed resistance to the first-line chemotherapy and increased risk of relapse [10]. Unfortunately, assessment of long-term responsiveness to combined chemotherapy of vinblastine and corticosteroid was not available in our case.

This case implied that LCH may be underdiagnosed in adults. Given the multiple differential diagnoses of neuroendocrine disorders, it is essential to be aware of this uncommon condition, especially in adults.

Ethics approval and consent for publication

This study was carried out in accordance with the Helsinki Declaration and approved by the Ethics Committee of Zhongnan Hospital,

Wuhan University. Written informed consent was obtained from the patient and her husband, including the permission for details and images related to the patient to be published.

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CRediT authorship contribution statement

Hanxing Liu: Visualization, Software, Investigation. **Yumin Liu:** Conceptualization, Project administration. **Hong Cao:** Validation, Resources, Investigation. **Yanping Liu:** Funding acquisition, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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