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CASE REPORT

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A case of multisystem Langerhans cell histiocytosis presenting as central diabetes insipidus

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare malignancy most commonly characterized by histiocytic infiltration of bone. LCH lesions in the skull place the adjacent central nervous system (CNS) at risk for involvement, which can manifest as central diabetes insipidus (CDI) when there is infiltration of the hypothalamic-pituitary axis. We present a case of a 39-year-old female who presented with polyuria and polydipsia for 1 year and left-sided hearing loss, gait instability, and nystagmus for 5 days. She was found on laboratory evaluation to have CDI and underwent left cortical mastoidectomy for a destructive peripherally enhancing mastoid lesion seen on MRI brain. Pathology revealed CD1a and S100+ LCH and the patient was subsequently discharged to begin outpatient chemotherapy with vinblastine and prednisone. The patient's CDI was diagnostic of CNS involvement, making her LCH multisystem through the infiltration of both the skull and hypothalamic-pituitary structures. As CDI can be seen in up to 25% of single-system LDH, and up to 50% of multisystem cases, radiologic studies to evaluate for osteolytic skull lesions must be considered as part of the evaluation for LCH when CDI has been diagnosed.

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1. Introduction

Langerhans cell histiocytosis (LCH) is a rare malignancy characterized by lesions of monoclonal histiocytes capable of infiltrating almost any organ system. This disease is also known by its previous monikers, Histiocytosis X and eosinophilic granulomas, or by its eponymous labels, Letterer–Siwe disease, Hand–Schüller–Christian disease, and Hashimoto–Pritzker disease. Even its own name is a potential misnomer, as recent studies have suggested that the malignant cell is actually a dendritic precursor from the bone marrow instead of a transformed Langerhans cell from the epidermis [1]. Largely a disease of children, its incidence in adults approximates 1–2 cases per million with a mean age of 35 ± 14 years at diagnosis [2]. LCH is classified based on organ involvement into single-system (usually bones or lungs in adults) versus multisystem disease. The latter is further stratified into low and high-risk groups, distinguished by the involvement of risk organs (the hematopoietic system, liver, and spleen) which carries worse prognoses [3,4].

There is skeletal system involvement in most cases, and LCH lesions within the skull place the disease within close proximity to the central nervous system (CNS). Lesions are deemed CNS-risk if they occur in the orbital, temporal, sphenoidal, ethmoidal, or mastoid bones or the paranasal sinuses or the anterior/middle cranial fossae. CNS involvement can manifest as central diabetes insipidus (CDI) through the infiltration of the hypothalamic-pituitary structures. CDI can be seen in up to 25% of all LCH cases, in multisystem disease the rate climbs up to 50% of the cases [5].

Diagnosis is biopsy-driven, with typical microscopic findings including granulomatous pathology with mononuclear cells with indented nuclei accompanied by lymphocytes and eosinophils. Confirmation of the diagnosis requires histological staining for markers such as CD1a and S100 [2]. Treatment is tailored to organ involvement and can range from surgical curettage to systemic chemotherapy. The latter is indicated for multisystem LCH, CNS-risk lesions, and particular cases of multifocal osseous involvement [4].

2. Case description

A 39-year-old female with a past medical history of Sjogren's syndrome on hydroxychloroquine, iron deficiency anemia, and hypothyroidism presented with polydipsia and polyuria for 1 year and left-sided hearing loss, nausea, and gait instability over the past 5 days. On physical exam, vital signs were stable. There were 3 beats of end-point horizontal nystagmus noted with left gaze. The rest of the cranial nerve exam was unremarkable. She had 5/5 muscle strength in the upper and

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lower extremities. Finger-to-nose and heel-to-shin tests were normal.

Initial laboratory workup revealed sodium 141 mmol/L, serum osmolality 301 mOsm/kg, urine osmolality 139 mOsm/kg, HbA1C 5.0%, and TSH 4.747 μIU/mL. A 24-hr urine volume was 9,750 mL. A water deprivation test was conducted, during which time urine osmolality remained 173 mOsm/kg but serum sodium increased to 146 mmol/L. Following an IV desmopressin 4 mcg injection, her urine osmolality peaked at 656 mOsm/kg and serum sodium decreased to 143 mmol/L. With central diabetes insipidus diagnosed, she was started on PO desmopressin 0.05 mg daily which caused complete resolution of her symptoms.

An MRI of the pituitary was unremarkable but incidentally showed an extra-axial mass that was explored further with an MRI brain. This subsequent imaging revealed bilateral extra-axial enhancing masses (1.5 × 0.8 cm lesion in the right parietal region and 3.4 × 0.8 cm lesion in the left parietal region), a destructive peripherally enhancing lesion in the left mastoid, and a few scattered small bright T2 nonspecific foci in the periventricular white matter. ENT and neurosurgery were consulted who proceeded with left cortical mastoidectomy for the radiographically destructive inflammatory lesion.

Pathology revealed Langerhans cell histiocytosis (LCH) and immunoperoxidase workup showed positive staining with CD1a and S100. She was discharged in stable condition and referred to hematology-oncology who ordered PET/CT scan which was remarkable for hypermetabolic lytic lesions involving the biparietal calvarium, left mastoid temporal bone, distal right clavicle, L2 vertebra, and left iliac wing. Of note, the lungs, liver, and spleen were not involved, and as the patient did not have cytopenias, bone marrow biopsy was not deemed necessary. She was subsequently started on chemotherapy with vinblastine and prednisone.

3. Discussion

The label Langerhans cell histiocytosis (LCH) derived from histologic studies of biopsied lesions. It was noted that the malignant histiocytes contain Birbeck granules and the protein langerin (CD207), both associated with Langerhans cells (LC), and it was postulated that the epidermal LC underwent a malignant transformation in LCH. However, a subsequent cytologic study illustrated that the dendritic cells that form LCH lesions are actually precursors from the bone marrow that travel to lesion sites and differentiate into langerin+ cells, a theory termed the 'Misguided Myeloid Dendritic Cell Precursor' model [1]. Animal studies confirmed the identity of LCH as a myeloid neoplasia by demonstrating that inducing a point mutation implicated in the disease's pathogenesis, *BRAF-V600E*, in bone marrow dendritic cell progenitors resulted in a phenotype mimicking high-risk LCH in humans, while inducing the same mutation in differentiated dendritic cells resulted in a low-risk LCH phenotype [6].

Our patient had multifocal bone disease, including a CNS-risk lesion in the left mastoid. Her central diabetes insipidus (CDI) is a diagnostic of CNS involvement, making her overall LCH multisystem. The circumventricular organs, including the posterior pituitary, are particularly vulnerable to LCH infiltration due to the absence of a blood-brain barrier. As our patient had an unremarkable MRI of her pituitary gland, the presence of CDI suggests that another part of the hypothalamic-pituitary axis was involved. Our patient was fortunate in that LCH was diagnosed soon after her CDI was detected, and in some cases, the LCH is discovered years after CDI manifests [7]. Eventually, anterior pituitary involvement can occur in up to 60% of LCH cases with CDI, causing further hormonal derangements. Additional patterns of CNS involvement include lesions of the cerebellum and brainstem as well as infiltration of the hypothalamus [5].

Treatment of LCH is dependent upon organ involvement and the extent of disease. Our patient had multisystem disease, involvement of a CNS-risk region, and multifocal bone disease, thus systemic therapy was indicated. Notably, she had no risk organ involvement, which improves her overall prognosis. She was placed on the vinca alkaloid vinblastine and prednisone. This chemotherapeutic regimen is standard therapy for children and was validated in a series of three pediatric clinical trials by the Histiocyte Society [8–10]. Seeking to examine its efficacy in adults, a recent multicenter retrospective study was conducted on 35 adult LCH patients: 80% with multisystem disease, 89% without risk organ involvement, and 40% with CDI. The cohort was treated with vinblastine 6 mg/m^2 for at least 6 weeks and prednisone 40 mg/m^2 (our patient was placed on an identical regimen). At the end of the treatment period, 71% of the patients had responded (defined as either complete resolution or regression); however, the disease did recur in 40% of this subset. The risk of reactivation/worsening was not affected by disease location or by the presence of multisystem disease [4]. Appropriate management of LCH-induced CDI involves prompt diagnosis as early intervention with chemotherapy can reverse CDI and prevent the later development of anterior pituitary hormonal deficiencies (APHD) or neurodegenerative disease [11].

Disclosure statement

No potential conflict of interest was reported by the authors.

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