

Endocrine Complications in Langerhans Cell Histiocytosis: A Case of Empty Sella Syndrome with Hypopituitarism

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare clonal myeloid neoplasia characterized by infiltration of CD1a+/CD207+ dendritic cells, frequently affecting bones, skin, and the central nervous system. Endocrine complications, particularly involving the hypothalamic-pituitary axis, are common in multisystem disease and may result in irreversible dysfunction, impacting growth, development, and overall quality of life. An 18-year-old male diagnosed with LCH at age 10 presenting with polyuria, polydipsia, and delayed puberty. He was found to have central diabetes insipidus, central hypothyroidism, hypogonadotropic hypogonadism, and a grade IV empty sella on brain MRI. The patient had a history of bone and soft tissue involvement and underwent chemotherapy for multisystem LCH. His current therapy includes desmopressin, levothyroxine, vitamin D, calcium supplementation, and planned to give testosterone replacement. This case illustrates the classic progression of endocrine complications in LCH with hypothalamic-pituitary axis involvement. Central diabetes insipidus is often the first manifestation followed by anterior pituitary hormone deficiencies. The finding of total empty sella on MRI likely reflects chronic inflammatory damage or pituitary atrophy. The combination of central diabetes insipidus (CDI), central hypothyroidism, and delayed puberty requires lifelong hormonal replacement and regular endocrine follow-up. The case also highlights the importance of addressing bone health and growth delays secondary to hormonal deficiencies and previous glucocorticoid therapy. Early identification and management of endocrine complications in LCH, particularly those involving the pituitary are essential to reduce morbidity and improve patient outcomes. Lifelong monitoring and multidisciplinary care are necessary for optimal management of LCH survivors.

Keywords: Langerhans cell histiocytosis, central diabetes insipidus, hypopituitarism, empty sella syndrome, hypogonadotropic hypogonadism, endocrine complications

INTRODUCTION

Langerhans cell histiocytosis (LLH) is a rare disease characterized by clonal expansion of myeloid precursors that differentiate into CD1a⁺/CD207⁺ in lesions. It can occur at any age with varying degrees of systemic involvement. With a median age upon diagnosis of 3 years, the reported incidence of LCH varies from 2.6 to 8.9 cases per million children under the age of 15 per year. The exact incidence of LCH in adults is much less defined: the only available data are for disseminated disease, with 0.07 cases per million per year. Despite the high cure rate, it can cause serious long-term neurological or endocrine consequences that might impair quality of life.¹

Recent advances in molecular pathogenesis have identified recurrent oncogenic somatic mutations in LCH that activate the MAPKinase (MAPK) pathway, with BRAF V600E mutation present in approximately 55% of cases. These mutations are associated with disease recurrence and high-risk presentations, confirming that LCH is a neoplastic disorder arising from an expansion of early myeloid cells with constitutive activation of the MAPK RAS/RAF/MEK/ERK cell signaling pathway.^{2,3}

Endocrine abnormalities from LCH include excessive thirst and urination caused by damage to the back part of the pituitary gland. This condition is known as diabetes insipidus. If the front part of the pituitary gland is damaged by LCH, the patient may have low levels of thyroid hormone, growth hormone, adrenal stimulating hormone and the hormones that lead to sexual maturation. Bone involvement in children or adults presents as painful areas which may be swollen. In children, the skull is most often affected, followed by long bones of the upper and lower extremity, ribs and spine.⁴

This case report describes an 18-year-old male patient with LCH who developed multiple endocrine complications including empty sella syndrome with CDI, delayed puberty, and

central hypothyroidism. The case highlights the importance of recognizing and managing these complications in the context of LCH to improve patient outcomes and quality of life.

CASE ILLUSTRATION

Patient Information

An 18-year-old male presented to the endocrinology clinic with complaints of polyuria and polydipsia. He had a history of LCH diagnosed at age 10 and was transitioning from pediatric to adult care.

Clinical Findings

The patient reported frequent urination more than 20 times per day with a 24-hour urine volume of approximately 4000 ml. He experienced increased thirst and consequently high fluid intake. He denied symptoms of fatigue, dizziness, hearing disturbances, anxiety, palpitations, muscle cramps, fever, bone pain, nausea, vomiting, or weight changes. He reported never experiencing ejaculation but had noted clear fluid discharge from his genitalia occasionally.

On physical examination, the patient's vital signs were stable: blood pressure 110/70 mmHg, heart rate 88 beats/minute, respiratory rate 18 breaths/minute, and temperature 36°C. His weight was 62.5 kg, height 164 cm, and BMI 23.2 kg/m² (normal weight). Notable findings included gynecomastia and Tanner stage 3 genital development with testicular volume of 8 cc.

Timeline and Diagnostic Assessment

The patient's clinical course began at age 10 when he first experienced polyuria and polydipsia, drinking up to 19 liters of water daily with urination frequency exceeding 20 times per day. Initial cranial CT and MRI showed no pituitary abnormalities, but CDI was diagnosed based on clinical symptoms and water deprivation test.

At age 12, he developed a mass in his right thigh. MRI was done and revealed a soft

tissue tumor with lytic lesions in the distal femur metaphysis. Soft tissue biopsy confirmed LCH via CD1a and CD207 immunohistochemical staining. He also frequently experienced generalized weaknesses and pain in the right shoulder. Laboratory tests showed hypothyroidism with thyroid-stimulating hormone (TSH) 8.663 μ IU/mL (reference range 0.35-4.94 μ IU/mL) and fT4 0.86 ng/dL (reference range 0.89-1.37 ng/dL) and no palpable thyroid enlargement. Imaging revealed soft tissue masses involving multiple muscles in the right shoulder region with destruction of the first right posterior rib. Chemotherapy was planned at that time but then delayed due to the patient's entry into a boarding school and later by the COVID-19 pandemic. He never had any treatment for 3 years later.

At age 15, new lesions appeared on his right chest, back, and armpit, which became painful. Bone marrow examination showed hyperactive reticuloendothelial system with hemophagocytosis. He then underwent 12 months of chemotherapy with the LCH protocol (vincristine, etoposide, prednisone), which led to resolution of the painful bone and soft tissue lesions and no evidence of new active disease on subsequent imaging. However, despite clinical remission of LCH, the patient developed long-term endocrine sequelae, including central diabetes insipidus, central hypothyroidism, and hypogonadotropic hypogonadism, suggesting irreversible hypothalamic–pituitary axis damage. During that time, he also experienced gynecomastia grade II with no galactorrhea (figure 1). Testosterone measured and the level was 2.72 nmol/L (reference range 4.94-32.01 nmol/L), Follicle-stimulating hormone FSH 5.4 mIU/mL (reference range 1.5-12.4 mIU/mL) and LH 2.8 mIU/mL (reference range 1.7-8.6 mIU/mL). MRI brain then performed and revealed empty sella grade IV (total empty sella) with thinning the pituitary gland (figure 2). Bone age assessment with Greulich-Pyle Method showed

a bone age of 15 years (chronological age 16.5 years) indicating delayed bone maturation. X-ray of lumbar-sacral vertebrae in 2 positions and thoracic vertebrae in 2 positions at age 17 showed decrease bone density suggested osteopenia and 25-OHD level 12.6 ng/mL showed vitamin D deficiency while ion calcium 0.94 mmol/L showed hypocalcemia. Chest CT scan at age 18 showed anterolateral rib 1 deformity. No obvious lesion or enhancement is seen around the lesion (figure 3).

Current Medications

The patient is currently managed with desmopressin 4-5 times 0.2 mg daily, levothyroxine 100 mcg daily (Monday-Thursday) and 150 mcg daily (Friday-Sunday), vitamin D3 1000 IU daily, and calcium carbonate 500 mg twice daily.

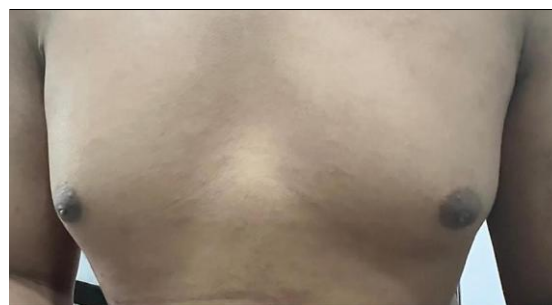


Figure 1. Gynecomastia grade II

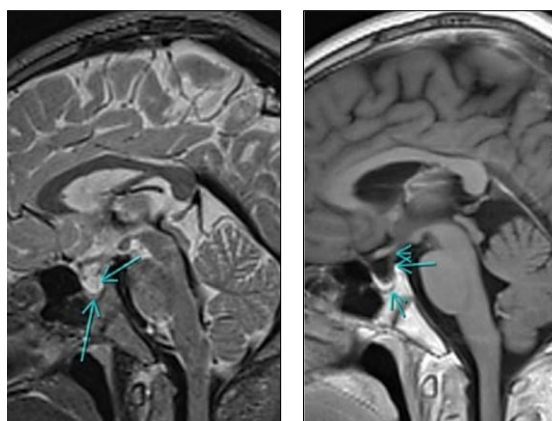


Figure 2. MRI findings are consistent with a grade IV empty sella, characterized by thinning of the pituitary gland and partial filling of the sella turcica with cerebrospinal fluid. The pituitary gland demonstrates homogeneous post-contrast enhancement, with no evidence of mass lesion, abnormal enhancement, or other intracranial pathology.

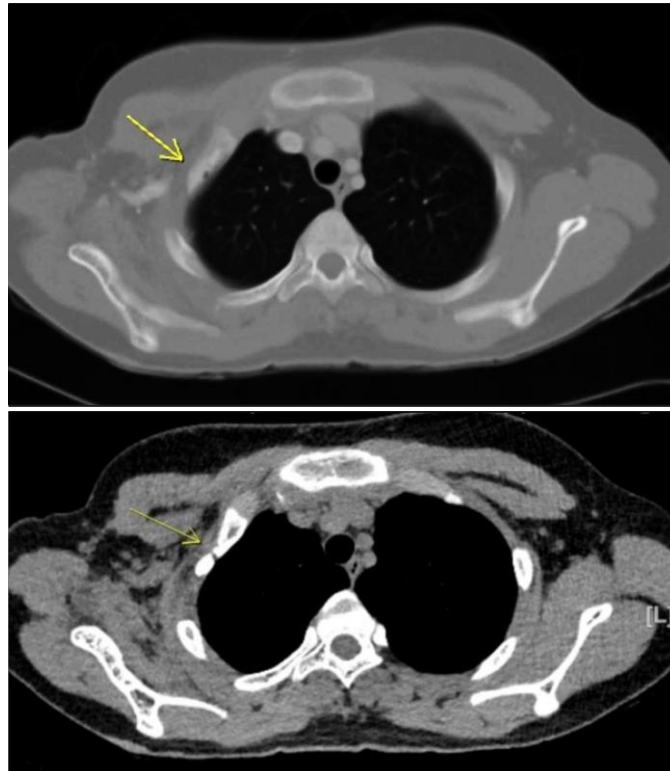


Figure 3. Right anterolateral rib 1 deformity. No obvious lesion or enhancement is seen around the lesion

DISCUSSION

LCH is now recognized as an inflammatory myeloid neoplasia with constitutive activation of the MAPK RAS/RAF/MEK/ERK cell signaling pathway. The MAPK pathway plays a vital role in regulating cell differentiation, proliferation, and apoptosis, particularly in myeloid cell differentiation and maturation. Genomic studies have identified recurrent somatic mutations in LCH, with BRAF V600E mutation present in approximately 55% of cases, while other mutations such as MAP2K1 (10-20%) and rare BRAF splicing mutations have also been reported.^{2,3}

The multisystem involvement with bone lesions and soft tissue masses is common characteristic of LCH. In our patients, LCH diagnosis is obtained from immunohistochemistry, and chemotherapy is performed for the treatment. Although BRAF V600E testing was unavailable,

MAPK pathway activation remains central to LCH pathogenesis, warranting targeted therapies (e.g., BRAF inhibitors) in refractory cases. The pathological progression aligns with the known disease pattern in LCH, where abnormal proliferation of histiocytes leads to tissue infiltration and damage.⁵

Central nervous system (CNS) involvement in LCH usually occurs with multisystem disease. It can be in the form of either focal mass lesions or progressive neurodegenerative disease. Among the CNS involvement, hypothalamic-pituitary involvement is the most common. CDI represents the most frequent endocrine manifestation observed in patients with LCH, which can present either as an isolated deficiency or in combination with other anterior pituitary hormonal dysfunctions. Across studies, the prevalence of CDI has a wide range, with as high as up to 94% in the presence of one or more other pituitary hormonal abnormalities. Among anterior pituitary dysfunction, growth hormone (GH) deficiency is the most common, with

a prevalence between 53% and 67%, and almost always occurs with CDI. This is followed by gonadotropin deficiency. Although isolated deficiencies have been reported, Central hypothyroidism and adrenal insufficiency are generally seen as a part of panhypopituitarism.⁶ As seen in our case, our patient's persistent polyuria and polydipsia require increasing doses of desmopressin (4-5 times 0.2 mg daily) indicate severe CDI. Once CDI develops, it becomes irreversible in most patients, who will require life-long desmopressin replacement therapy. The MRI finding of total empty sella in LCH further supports the correlation with chronic pituitary stalk inflammation and atrophy, as seen in neurodegenerative LCH variants. In LCH, this can result from direct infiltration and subsequent atrophy or from inflammatory processes affecting pituitary.^{7,8}

The patient's central hypothyroidism, evidenced by laboratory result and his requirement for levothyroxine supplementation is another manifestation of pituitary dysfunction. Central hypothyroidism occurs due to insufficient TSH production by the anterior pituitary gland.⁶ Delayed puberty, as manifested by Tanner stage 3 genital development with testicular volume of 8 cc at age 18 is consistent with hypogonadotropic hypogonadism, another consequence of anterior pituitary dysfunction. Normally, puberty should begin by age 14 in males, with progression through Tanner stages occurring over 2-5 years. The patient's bone age of 15 years at chronological age 16.5 years further confirms the developmental delay associated with his endocrine dysfunction.⁹ Testosterone therapy will be performed to induce puberty and reduce complications due to its deficiency. It is routinely prescribed in adolescent males with constitutional delay of growth and puberty or hypogonadism. Testosterone plays a critical role in male sexual development and function.

It has numerous effects on various tissues and systems. These include the acceleration of linear growth during adolescence, a positive effect on bone mass and accretion, and changes in body composition associated with an increase in lean mass and a reduction and redistribution of fat mass.¹⁰

The presence of gynecomastia in this patient likely resulted from prolonged glucocorticoid therapy (prednisone) during chemotherapy for LCH. Glucocorticoids can disrupt the estrogen- testosterone balance, leading to breast tissue enlargement. Additionally, central hypothyroidism and delayed puberty (due to hypothalamic-pituitary dysfunction from empty sella) may contribute to hormonal imbalances, though the primary cause here is prolonged glucocorticoid therapy. Osteopenia, documented in the lumbar spine X-ray, may result from multiple factors including the underlying inflammatory disease, endocrine dysfunction (particularly hypothyroidism and hypogonadism), and possibly glucocorticoid therapy received during chemotherapy.¹¹⁻¹² These manifestations likely result from both hypothalamic-pituitary involvement and the cumulative toxic effects of systemic therapy. Consequently, chemotherapy may indirectly impair linear growth, pubertal progression, and bone mineralization, even after disease remission.¹³ Vitamin D deficiency and hypocalcemia in these patients may increase the risk of osteoporotic fractures, especially in the hip. Vitamin D deficiency does not only cause weaker bones due to osteomalacia, but also severe myopathy with loss of muscle strength, selective loss of the rapid type-2 fibres, dyscoordination and consequently increased propensity for falls. It is therefore not surprising that meta-analyses indicate that correction of vitamin D deficiency results in a decreased fall and fracture risk. Daily intake of 400 IU/day is not sufficient, while 800 IU/day reduces falls and fractures significantly. Several reviews have

emphasized the need of addition of calcium to vitamin D for fracture prevention and a dose of calcium 1,000 to 1,200 mg/day was suggested; both vitamin D and calcium therapies has been given to this patient.¹⁴

A recent multicenter cohort study involving 219 adult patients with LCH demonstrated a 5-year OS rate of 88.7% and a 10-year OS rate of 74.5%, with the median OS not yet reached. The presence of risk-organ involvement (liver, spleen, bone marrow) was associated with significantly poorer outcomes (hazard ratio 10.8), while age at diagnosis also influenced prognosis. In contrast, BRAF V600E mutation status was not associated with OS or progression-free survival. Most LCH-related deaths occurred within the first five years after diagnosis, whereas later mortality was mainly attributed to non-LCH causes such as secondary malignancies, chronic obstructive pulmonary disease, and cardiovascular disease. Consequently, although the disease-specific prognosis is generally favorable, adult LCH survivors remain at higher long-term mortality risk compared with the general population (standardized mortality ratio 2.66). These findings highlight the need for lifelong multidisciplinary follow-up, focusing on prevention of late complications, metabolic health, and endocrine sequelae. In our patient, the absence of new lesions and stable imaging indicate remission, while persistent panhypopituitarism reflects irreversible hypothalamic–pituitary injury requiring lifelong hormonal replacement.¹³

CONCLUSION

This case highlights the complex and multifaceted endocrine complications associated with LCH, particularly when involving the hypothalamic-pituitary axis. Empty sella syndrome with CDI, delayed puberty, and central hypothyroidism are serious long-term sequelae that significantly impact quality of life and require

timely diagnosis and ongoing multidisciplinary management. Early recognition of endocrine dysfunction in patients with LCH is crucial for prompt intervention and to prevent further complications. Comprehensive follow-up with endocrine evaluation including annual pituitary MRI, Dual-Energy X-ray Absorptiometry (DEXA scans), and hormonal panels is critical for LCH survivors, especially those with multisystem involvement or central nervous system lesions. Because LCH frequently develops during childhood, endocrine function should be assessed at diagnosis and re-evaluated periodically every 6–12 months throughout growth and puberty to allow early detection and management of evolving pituitary deficiencies.

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