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SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TÜRKİYE

A Case of Langerhans Cell Histiocytosis Presenting with Suprasellar Mass and Panhypopituitarism Clinic

CASE REPORT
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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease involving multiple systems, and it is caused by excessive proliferation of Langerhans cells. The hypothalamic-pituitary region (HPR) is involved in 5%-50% of all LCH patients, particularly those with multifocal disease. Diabetes insipidus (DI), the most common endocrinal abnormality, occurs in 15%-50% of patients with HPR-LCH. Anterior pituitary deficiency occurs in the minority, in 5%-20% of the patients, usually in combination with DI. The disease is clinically heterogeneous. The most commonly involved organs are the skeleton (78.7%) and skin (36.7%). Involvement of multiple organs such as the skin, lymph nodes, lungs, spleen, liver, bone marrow, ear, nose, and throat is a criterion for poor prognosis. We report a 19-year-old woman who presented with a pituitary suprasellar mass, had anterior pituitary deficiency (APD) but no DI at the time of diagnosis, and had the ear and mastoid bone involvement. We initially did not consider LCH but diagnosed it later. In the literature, we found only 2 cases with APD but without DI among patients with an LCH diagnosis. The clinical features of HPR-LCH are similar to other hypothalamic-pituitary disorders; thus, differential diagnosis is necessary. Accurate and rapid diagnosis is crucial for HPR-LCH; its symptoms are progressive and irreversible. Unlike other disorders of HPR, LCH is treated with chemotherapy. Necessary surgical interventions must be performed to make a rapid pathologic diagnosis.

Keywords: Langerhans cell histiocytosis, suprasellar mass, panhypopituitarism

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease involving multiple systems and is caused by excessive proliferation of Langerhans cells.[1] Langerhans cell histiocytosis of the hypothalamic-pituitary region (HPR) is rarely diagnosed in patients with LCH.[2] It is often diagnosed in childhood.[3] The proportion of adult cases is less than 30% of all cases. A prevalence of 1.8 per million has been reported.[4]

Langerhans cell histiocytosis is classified into localized and multifocal forms. Localized LCH is defined as the involvement of one soft tissue with or without the involvement of the skeletal system. In contrast, the multifocal form refers to the involvement of two or more soft tissues regardless of the skeletal system's involvement.[5] The disease is clinically heterogeneous. The most commonly involved organs are the skeleton (78.7%) and skin (36.7%). Involvement of multiple organs such as the skin, lymph nodes, lungs, spleen, liver, bone marrow, ear, nose, and throat is a criterion for poor prognosis.[6]

The HPR is involved in 5%-50% of all LCH patients, particularly those with multifocal disease.[7] Diabetes insipidus (DI), the most common endocrinal abnormality, is observed in 15%-50% of the patients with HPR-LCH, whereas pituitary deficiency is observed in the minority in 5%-20% of the patients, usually in combination with DI.[6,7]

In a study of 274 adult patients with LCH diagnosed by biopsy, DI was found in 81 (29.6%) patients.[8] In a study conducted from 2007 to 2015 involving patients with LCH and isolated involvement of HPR, all cases initially presented with DI. Anterior pituitary deficiency (APD) was rarely detected.[9]

The definitive diagnosis of LCH is made by histopathologic examination. The presence of Birbeck granules in electron microscopy and positive staining for CD68, S100, Langerin, and CD1a in immunohistochemical staining confirms the diagnosis of LCH.[9]

Hypothalamic-pituitary region–Langerhans cell histiocytosis is a rare disease that is difficult to diagnose and highly likely to be misdiagnosed. We report a case of LCH presenting with a

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suprasellar mass and panhypopituitarism and without DI to reduce the rate of misdiagnosis and enhance clinical experience. Written informed consent was obtained from the patient.

Case Presentation

A 19-year-old woman presented to the neurosurgery outpatient clinic with complaints of headache, blurred vision, and menstrual irregularities. Pituitary magnetic resonance imaging (MRI) revealed a suprasellar mass and optic chiasm glioma, and trans-sphenoidal surgery (TSS) was scheduled. The patient was referred to the endocrinology outpatient clinic for preoperative endocrinological evaluation.

In the patient's history, she presented to the pediatric endocrinology outpatient clinic 4 years ago because of menstrual irregularity, where she was diagnosed with hypogonadotropic hypogonadism, and oral contraceptive (OC) treatment was initiated. Other anterior pituitary hormones were within normal range in the tests performed during that period. A pituitary MRI performed during the same period revealed a 9.5 × 9 mm microadenoma, and she was followed up with diagnoses such as Rathke cleft cyst and nonfunctioning pituitary microadenoma. Subsequently, the patient did not follow-up and intermittently used OC treatment.

She had grade II mitral valve regurgitation secondary to acute rheumatic fever and Sydenham's chorea in her medical history. She also had a history of frequent antibiotic therapy for chronic otitis media for the last 2 years. She was on a regular monthly course of depot penicillin. She was taking 0.03 mg ethinyl estradiol and 3 mg drospirenone occasionally. She stated that her menstrual cycle was regular during the periods when she was using OCs.

She had her first menstrual bleeding at the age of 14. On physical examination, breast development and pubic hair were evaluated as Tanner stage 5. She was 157 cm tall and weighed 68 kg. Her mother's height was 158 cm, and her father's height was 170 cm. Based on her parents' heights, she had the target height, which was calculated to be 157 ± 7 cm. The visual field was normal, with minimal contrast losses.

There was no polyuria or polydipsia. Serum sodium level and urine density were normal. Laboratory test results of hemogram, glucose, electrolytes, urea, creatinine, and liver function were within normal range. The following are her anterior pituitary hormone levels: serum free thyroxine (f-T4), 0.6 ng/mL (0.80-1.90); thyroid-stimulating hormone (TSH), 2.76 µIU/mL (0.27–4.2); morning growth hormone (rGH), 0.1 ng/mL; insulin-like growth factor-1 (IGF-1), 35 ng/mL (127–424); cortisol at 08:00, 3.3 µg/dL (10-20); adrenocorticotropic hormone (ACTH), 74 pg/mL (0-63); low-dose (1 µg) ACTH stimulation test, 2/12/11 µg/dL; luteinizing hormone (LH), <0.1 IU/mL (3–12); follicle-stimulating hormone (FSH), <0.4 IU/mL (2–10); and estradiol, <5 ng/dL. Slightly elevated serum prolactin level of 47 ng/mL (0-25) was considered due to stalk compression. The endocrine functions of the patient were consistent with hypogonadotropic hypogonadism, central hypothyroidism, central hypocortisolemia, and growth hormone (GH) deficiency. Hydrocortisone 20/10/10 mg was started, followed by levothyroxine 75 µg 1 × 1.

On pituitary MRI (Figure 1), a solid mass lesion with a size of 24 × 15 × 19 mm (optic chiasm glioma? hamartoma?) with diffuse contrast in the suprasellar region, the widest part of the area extending from the stalk to the mammillary body compressing the optic nerve bilaterally was observed. In addition, there were heterogeneous hyperintense signal increases in T2A in bilateral mastoid region localization (Figure 2).

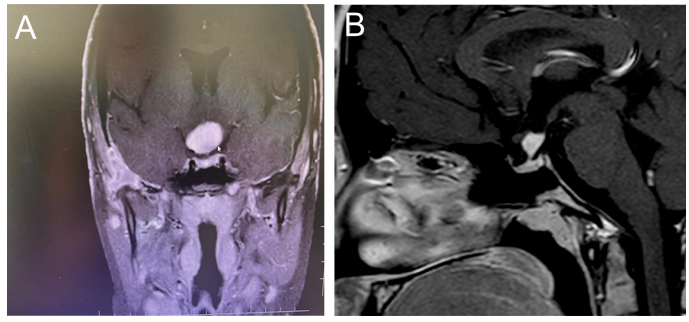

Figure 1. Pituitary magnetic resonance imaging at diagnosis and before chemotherapy (A, coronal slice; B, sagittal slice).

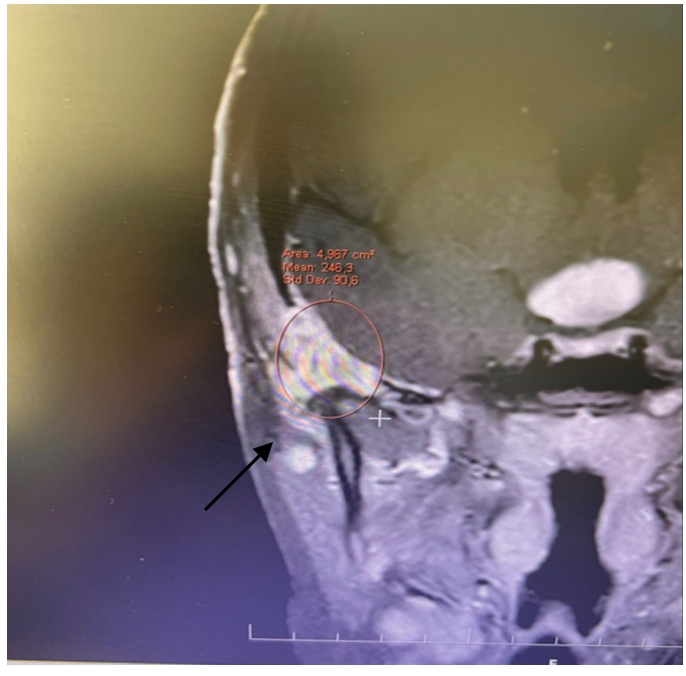

Figure 2. Heterogeneous hyperintense signal increases in the left mastoid region in pituitary magnetic resonance imaging.

MAIN POINTS

- Patients with a suprasellar tumor and anterior pituitary deficiencies (APD) require a thorough physical examination and medical history.
- A history of hearing loss and chronic otitis media can indicate Langerhans cell histiocytosis (LCH) in the differential diagnosis.
- Although uncommon, LCH should be considered in individuals with APD and a suprasellar mass who do not have diabetes insipidus.
- Since the symptoms of hypothalamic-pituitary region (HPR)-LCH are progressive and irreversible, an accurate and timely diagnosis is essential.
- In contrast to other HPR illnesses, chemotherapy is used to treat LCH. A timely pathologic diagnosis should be made by performing any necessary surgical procedures.

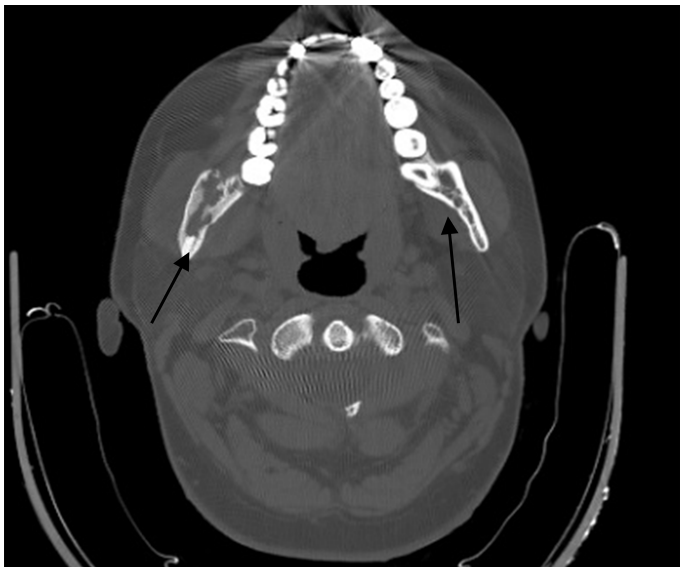

Figure 3. Multiple lytic lesions in both temporal bones on temporal computed tomography.

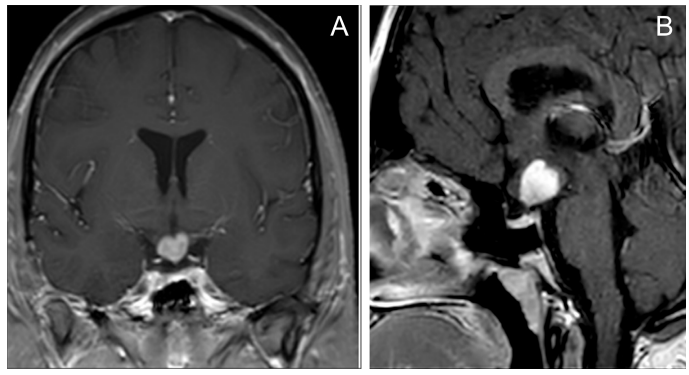

Figure 4. Pituitary magnetic resonance imaging after 3 cycles of chemotherapy treatment (A, coronal slice; B, sagittal slice).

The patient, who had been suffering from ear pain and decreased hearing for the last year and was evaluated as chronic otitis with frequent otolaryngology department admission, was admitted to the otorhinolaryngology polyclinic and temporal computed tomography (CT) was taken there. On temporal CT (Figure 3), multiple lytic lesions on bilateral temporal bones, mastoid levels, calvarial bones, temporomandibular joint levels, and mandibular condyle section on the right were evaluated together with mass lesion findings showing an increase in size in the suprasellar area. The case was primarily assessed as metastasis of LCH in the differential diagnosis, and LCH was considered. The patient was referred to the hematology department. Bone marrow aspiration and biopsy revealed mild hypocellular bone marrow, and no neoplasm was observed. Subsequently, the mastoidectomy cavity was debrided. CD68, S-100, Langerin, and CD1a were immunohistochemically positive, consistent with LCH. The patient's APD was evaluated to be caused by HPR-LCH. Owing to bone and ear involvement, the patient was considered to have multifocal LCH, and a chemotherapy regimen consisting of 6 cycles of methotrexate + vinblastine + methylprednisolone was scheduled, which led to significant regression (13 × 7 × 14 mm) in the pituitary mass on the pituitary MRI taken after the third cycle of chemotherapy (Figure 4). The following are her anterior pituitary hormone levels after the third cycle of chemotherapy: serum free thyroxine (f-T4), 1.09 ng/mL (0.80-1.90); TSH, 0.38 µIU/mL (0.27-4.2); morning GH (rGH), 0.16 ng/mL; IGF-1, 123 ng/mL (127-424); LH, 0.15 IU/mL (3-12); FSH,0.96 IU/mL (2-10); and estradiol, 7.7 ng/dL; serum prolactin level of 32 ng/mL (0-25). There was no significant change in the patient's anterior pituitary hormones after chemotherapy. The cortisol axis could not be evaluated because the patient received steroid treatment by the chemotherapy protocol. IGF-1 increased compared to before chemotherapy. Hypogonadotropic hypogonadism continued. The patient was euthyroid under levothyroxine replacement. It was planned to be evaluated entirely after her chemotherapy was completed.

Discussion

Langerhans cell histiocytosis is an inflammatory myeloid malignancy with mixed cell types caused by the infiltration of $CD1a^{+}/CD207^{+}$ dendritic cells into various tissues. The inflammatory and clonal nature of LCH is due to the somatic activating gene mutations in the mitogen-activated protein kinase pathway. Langerhans cell histiocytosis is considered a myeloid neoplastic disease as these mutations have hematopoietic precursors.[1]

Langerhans cell histiocytosis occurs most commonly in childhood and is a rare disease among adults. The central nervous system and HPR may be affected in the multifocal form of the disease. In patients with known multifocal LCH, a mass seen on pituitary MRI is usually considered sufficient for the involvement of HPR.[10] In our case, involvement of the ear and mastoid bone was simultaneously detected with the involvement of HPR; thus, multifocal LCH was considered in our patient. The suprasellar mass was considered an involvement of the LCH; thus, TSS was not initially considered, and a bone marrow aspiration biopsy was performed. When no diagnosis could be made, mastoid bone debridement was performed, and the histopathologic diagnosis was made.

Langerhans cell histiocytosis of the HPR occurs rarely. In 2010, the French national registry recorded 1236 patients with LCH under 18 years of age. Only 4 (0.32%) of 1236 patients with LCH had isolated HPR lesions.[11] In a retrospective study by Howarth that included 314 patients with LCH, 44 patients had multifocal LCH with the involvement of HPR, and only 2 patients had isolated involvement of HPR. All patients with HPR-LCH had DI.[12] Our patient presented to the clinic with APD and a suprasellar mass and did not have DI; thus, LCH was not initially considered among differential diagnoses. Anterior pituitary deficiency has not been evaluated in most studies because it is rare, and HPR involvement of LCH is usually detected first with the clinical presentation of DI. Anterior pituitary deficiency is generally diagnosed after surgery, radiotherapy, and chemotherapy are performed to treat LCH; therefore, the diagnosis is missed or delayed. In our case, APD was detected before diagnosing LCH, as the patient initially presented with the effects of suprasellar mass and APD. In a case report by Radojkovic et al,[13] the patient presented with visual field loss and APD due to suprasellar mass and was diagnosed with LCH following TSS, which was similar to our case. The patient had no DI, as in our case. Unlike our case, the case of Radojkovic et al. had isolated HPR involvement. Tabarin et al[14] reported a patient with hypothalamic LCH with APD and without DI, similar to our case. However, unlike ours, they evaluated it as multifocal and not isolated LCH because of skin involvement. In the literature, we found only 2 cases with HPR involvement and APD without DI. Our report is the

Table 1. Reviewed Cases of Langerhans Cell Histiocytosis of the Suprasellar Region

Author	Age	Sex	APD	DI	TME	Radiological Findings	Systemic	Localized
Radojkovic et al[13]	31	F	Yes	No	Yes	A suprasellar mass close to the optic chiasm, measuring 15 × 15 × 13 mm, expanding to the sella turcica and causing pituitary stalk encasement.	No	Yes
Tabarin et al[14]	NA	NA	Yes	No	NA	The tumor mimicked a chiasm glioma	Yes	No
Present case	19	F	Yes	No	No	A solid mass lesion with a size of 24 × 15 × 19 mm within the suprasellar region	Yes	No
Asano et al[15]	24	F	No	Yes	No	Enlarged pituitary stalk, thick under the optic chiasma	No	Yes
Horn et al[16]	18	M	Yes	Yes	No	Mass in the infundibulum (10 mm)	No	Yes
Ghafoori et al[17]	16	F	Yes	Yes	Yes	15 × 15 × 9 mm mass lesion in the sellar region.	No	Yes

APD, anterior pituitary dysfunction; DI, diabetes insipidus; TME, tumor mass effects; NA, not available.

third case. There are several patients presented in the literature who had APD and DI when LCH was diagnosed. In Table 1,[13-17] we have arranged the cases with and without DI diagnosed with LCH and a suprasellar mass.

The most common hormone deficiencies in patients with HPR-LCH are GH, gonadotropin (53%-58%), and TSH (3.9%) deficiencies in the order of frequency.[11] In our case, we detected GH deficiency, hypogonadotropic hypogonadism, central hypothyroidism, and central hypocortisolemia during the diagnosis, which was consistent with the literature. We considered the moderately increased prolactin levels to be due to stalk compression. The suprasellar mass in the MRI findings in our case was interpreted as optic chiasm glioma (?) and hamartoma (?), and we did not initially consider LCH in the patient. The signal increases in the mastoid region on the first pituitary MRI should have been alarming. Langerhans cell histiocytosis was considered because of mastoid bone involvement detected as a result of the patient's simultaneous presentation to the otorhinolaryngology outpatient clinic and the resulting temporal CT scan performed as the patient had a history of hearing loss and chronic otitis media.

Magnetic resonance imaging findings of HPR-LCH include absence of signal in the posterior pituitary region, thickening of the pituitary stalk, and suprasellar mass lesion. These findings may also be observed in diseases such as lymphocytic hypophysitis, lymphocytic infundibulo-neurohypophysitis, sarcoidosis, germ cell tumors, Rathke cleft cyst, ectopic pituitary adenoma, craniopharyngioma, and meningioma. Differential diagnosis with LCH should be made.[18] Our case presented with a suprasellar mass lesion and APD during the initial presentation, and diagnoses such as optic chiasm glioma and hamartoma were considered.

The pathological diagnosis of LCH is based on detecting Langerhans cells and CD1a and Langerin positivity. CD1a is an important immunohistochemical marker in the diagnosis of LCH. However, if CD1a and Langerin tests cannot be evaluated clearly, S100 positivity is significant for the diagnosis.[9]

The pathological diagnosis of isolated LCH-HPR is difficult. It is necessary to obtain a sufficiently large biopsy. The lesions to be biopsied are usually surrounded by important structures such as the hypothalamus, pituitary stalk, optic nerve, and superior hypophyseal artery. The larger the size of the biopsy specimen, the greater the likelihood of damage to adjacent structures and complications. In the previous case studies reported, TSS or craniotomy was performed to diagnose LCH-HPR.[2] Our case was multifocal, and the mastoid bone was involved in addition to the pituitary gland, so mastoid bone debridement was performed to reach the diagnosis.

In conclusion, patients presenting with a suprasellar mass and APD should undergo a complete physical examination, and a good medical history should be taken. In our case, LCH was not initially considered because of the absence of DI. The complaints of chronic otitis media and decreased hearing were not emphasized much. The diagnosis of LCH resulted from simultaneous ear, nose, and throat examination and temporal CT scan. The clinical features of HPR-LCH are similar to those of other hypothalamo-hypophyseal disorders and require differential diagnosis. Accurate and rapid diagnosis is crucial for HPR-LCH, as its symptoms are progressive and irreversible. Unlike other diseases of HPR, LCH is treated with chemotherapy. Necessary surgical interventions should be performed to make a rapid pathologic diagnosis.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.T.; Design – E.T., N.Y.; Supervision – D.T.; Materials – E.T., N.Y.; Data Collection and Processing – E.T., M.Ş.; Analysis and Interpretation – E.T., M.Ş.; Literature Review – E.T., D.T.; Author – E.T.; Critical Review – D.T.

Declaration of Interests: The authors have no conflicts of interest to declare.

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References

1. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379(9):856-868. [CrossRef]
2. Oda Y, Amano K, Seki Y, et al. Clinical features and difficulty in diagnosing Langerhans cell histiocytosis in the hypothalamic-pituitary region. *Endocr J*. 2022;69(4):441-449. [CrossRef]
3. Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. Writing Group of the Histiocyte Society. *Lancet*. 1987;1(8526):208-209.
4. Malpas JS. Langerhans cell histiocytosis in adults. *Hematol Oncol Clin North Am*. 1998;12(2):259-268. [CrossRef]
5. Gramatovici R, D'Angio GJ. Radiation therapy in soft-tissue lesions in histiocytosis X (Langerhans cell histiocytosis). *Med Pediatr Oncol*. 1988;16(4):259-262. [CrossRef]
6. Donadieu J, Thomas C, Brugieres L, et al. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child*. 1996;75(1):17-24. [CrossRef]

7. Dunger DB, Broadbent V, Yeoman E, et al. The frequency and natural history of diabetes insipidus in children with Langerhans-cell histiocytosis. *N Engl J Med*. 1989;321(17):1157-1162. [CrossRef]
8. Aricò M, Girschikofsky M, Généreau T, et al. Langerhans cell histiocytosis in adults. Report from the International Registry of the Histiocyte Society. *Eur J Cancer*. 2003;39(16):2341-2348. [CrossRef]
9. Huo Z, Lu T, Liang Z, et al. Clinicopathological features and BRAF(V600E) mutations in patients with isolated hypothalamic-pituitary Langerhans cell histiocytosis. *Diagn Pathol*. 2016;11(1):100. [CrossRef]
10. Isoo A, Ueki K, Ishida T, et al. Langerhans cell histiocytosis limited to the pituitary-hypothalamic axis—two case reports. *Neurol Med Chir (Tokyo)*. 2000;40(10):532-535. [CrossRef]
11. Kurtulmus N, Mert M, Tanakol R, Yarman S. The pituitary gland in patients with Langerhans cell histiocytosis a clinical and radiological evaluation. *Endocrine*. 2015;48(3):949-956. [CrossRef]
12. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ. Langerhans cell histiocytosis. Diagnosis, natural history, management, and outcome. *Cancer*. 1999;85(10):2278-2290. [CrossRef]
13. Radojkovic D, Pesic M, Dimic D, et al. Localized Langerhans cell histiocytosis of the hypothalamic-pituitary region: case report and literature review. *Hormones (Athens)*. 2018;17(1):119-125. [CrossRef]
14. Tabarin A, Corcuff JB, Dautheribes M, et al. Hystiocytosis X of the hypothalamus. *J Endocrinol Investig*. 1991;14(2):139-145.
15. Asano T, Goto Y, Kida S, Ohno K, Hirakawa K. Isolated histiocytosis X of the pituitary stalk. *J Neuroradiol*. 1999;26(4):277-280.
16. Horn EM, Coons SW, Spetzler RF, Rekate HL. IsolatedLangerhans cell histiocytosis of the infundibulum presenting with fulminant diabetes insipidus. *Childs Nerv Syst*. 2006;22(5):542-544. [CrossRef]
17. Ghafoori SH, Mohseni SH, Larijani B, Mohajeri-Tehrani MR. Pituitary stalk thickening in a case of Langerhans cell histiocytosis. *Arch Iran Med*. 2015;18(3):193-195.
18. Jian F, Bian L, Sun S, et al. Surgical biopsies in patients with central diabetes insipidus and thickened pituitary stalks. *Endocrine*. 2014;47(1):325-335. [CrossRef]