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Clinical report

Dumbbell-shaped primary CNS lymphoma involving the hypothalamus and pituitary gland

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Background: Primary central nervous system lymphoma (PCNSL) involving the hypothalamus and pituitary gland is extremely rare. Therefore, no case to our knowledge has been reported to date.
Objective: We described our findings in a 48-year-old immunocompetent man, who presented with four months progressive diabetes insipidus (DI) and two months subsequent headache.
Methods and Results: A radiological study and magnetic resonance imaging (MRI) suggested a homogeneous enhancing dumbbell-shaped lesion, 2.4□1.2 cm in size, involving both the hypothalamus and pituitary gland. A brain biopsy was conducted through a transnasal transsphenoidal approach, and a final histopathological diagnosis of the tumor was confirmed as diffuse large B-cell malignant lymphoma. After extensive tumor surveys, including computed tomography, MRI, ultrasound, bone marrow biopsy, lumbar puncture, and positron emission tomography (PET), no evidence of other lesions found. Subsequently, he received six cycles of intravenous high-dose methotrexate-based chemotherapy followed by one cycle of whole-brain radiotherapy. The progressive DI and headache completely resolved and he was in good health 11 months later.
Conclusion: Clinicians should consider the possibility of PCNSL in non specific clinical presentations.

***Keywords*:** CD20, dumbbell-shaped, methotrexate, primary central nervous system lymphoma, whole-brain radiotherapy

Primary central nervous system lymphoma (PCNSL) most frequently occurs in the cerebral hemisphere, basal ganglia, corpus callosum, or periventriclular region [3]. Clinical and radiological manifestations depend on the location and size of the lymphoma. PCNSL involving the hypothalamus, pituitary stalk, or pituitary gland with hypopituitarism in adult immunocompetent patients is very rare and only sporadic cases have been reported [7, 8, 11, 12]. However, to our best of knowledge, PCNSL involving these areas simultaneously, with a dumbbell-shaped image, has not previously been reported in the English-language literature.

Case report

A 48-year-old man was transferred to our department on May 17, 2010, with a history of four months progressive diabetes insipidus (DI) and two months of headache. On physical and neurological examination, his vision was normal, and no hemianopsia or symptoms of endocrine disturbances were observed. His past medical history was unremarkable. Computed tomographic angiography (CTA) revealed a slightly homogeneously enhancing lesion in the suprasellar cistern without ventriculomegaly or bone destruction (**Figure 1C**). Magnetic resonance imaging (MRI) of the brain displayed a 2.4 × 1.2-cm dumbbell-shaped lesion involving both the hypothalamus and the pituitary gland. The lesion was isointense (**Figure 1A**) on T1-weighted images, and homogeneously enhanced by gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (**Figure 1B**) with no involvement of the cavernous sinuses or internal carotid artery. The dumbbell-shaped lesion, abutting the optic tract and optic chiasma anteriorly, occupied the floor of the third ventricle and extended along the pituitary stalk to the pituitary fossa, while normal pituitary tissue was seemingly pressured and located at the sellar floor. Related laboratory findings demonstrated that the initial pituitary-gland axis hormones levels were

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decreased, except for prolactin (PRL), which was increased slightly at 33.10 ng/ml. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were low (FSH, 0.27 mIU/ml; LH, <0.10 mIU/ml), while TSH, ACTH, and GH were all normal (**Table 1**). HIV, hepatitis B and C, and syphilis were excluded by serology tests. Thus, a sellar mass was initially diagnosed, with the impression of non-pituitary etiology.

The patient underwent a transnasal trans-sphenoidal biopsy of the sellar mass and subsequent histopathological examination of the surgical specimen showed neoplastic cells with abundant cytoplasm and polymorphic nuclei with considerable mitotic activity (**Figure 2**). Immunohistochemistry indicated that the membranes were diffusely immunopositive for CD20, the cytoplasm was strongly immunopositive for CD79a, and the nuclei were scattered immunopositive for PAX5. These specific B-lymphocyte markers all indicated that the neoplastic cells were of B-cell origin, while specific T-lymphocyte markers were all negative (including CD3 and CD43). Thus, a diagnosis of diffuse large B-cell lymphoma (DLBCL) was made.

To confirm whether the CNS lymphoma was primary or secondary to a systemic lymphoma, additional examinations were performed. A CT scan of his chest, abdomen, and pelvis, ultrasound examinations of the neck, axillary, inguinal, and retroperitoneal lymph node, and testicles, positron emission tomography (PET) scan of the whole body, all showed no evidence of systemic lymphoma. Primary intraocular lymphomas were also excluded from negative results of a slit-lamp examination. A subsequent bone marrow biopsy was negative for any hematological disease. A lumbar puncture was performed and no cytopathological abnormality was found in the cerebrospinal fluid (CSF). CSF and serum tumor markers, such as alpha-fetoprotein (αFP), ferritin, Epstein–Barr virus antibody, and beta human chorionic gonadotropin (□HCG) levels, were all within normal limits. Finally, we decided on a diagnosis of PCNSL, involving the pituitary and hypothalamus simultaneously with a dumbbell-shaped imaging.

The patient subsequently received a chemoradiation schedule. After six cycles of intravenous high-dose methotrexate-based regimens (3.5 g/m^2 as a four to six hours infusion given every 20 days) and one cycle of whole-brain radiotherapy (40 Gy to the whole brain, 2 Gy/day × 20 days) was followed as consolidation therapy, the initial progressive diabetes insipidus and headache resolved fully. Radiological remission of the lesion was also achieved (Figure 1d). To date, the patient is still under regular follow-up and is in good health at 11 months, with no evidence of local or systemic recurrence.

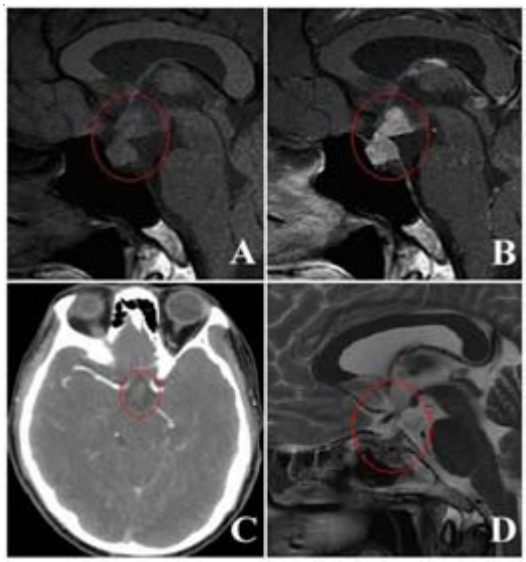

Figure 1. **A:** (sagittal) Preoperative T1-weighted image revealed a dumbbell-shaped lesion occupying the pituitary fossa; it was isointense. **B:** (sagittal) Preoperative T1-weighted image revealed the lesion was homogeneously enhanced by gadolinium, showing involvement in the hypothalamus and pituitary gland. **C:** (axial) Preoperative CTA revealed a slightly homogeneously enhanced lesion in the suprasellar cistern. **D:** (sagittal) 11 months postoperative T2-weighted image revealed radiological remission of the lesion, with no recurrence.

Table 1. Initial laboratory testing values of the pituitary gland axis hormones.

Pituitary hormones	Value		Reference Range	Target Gland Hormones	Value		Reference Range
TSH	0.703		0.400-4.00 mIU/L	Free T4	4.7	↓	10.30-24.45 pmol/L
ACTH	5.8		6.0-46.0 pg/ml (8am)	Cortisol	<1.0	↓	5.0-25.0 μg/dL (8am)
FSH	0.27	↓	1.27-12.96 mIU/mL (Adult male)	Testosterone	<20.0	↓	175-781 ng/dL (Adult male)
LH	<0.10	↓	1.24-8.62 mIU/mL (Adult male)				
GH	0.51		0.06-5.00 ng/ml				
PRL	33.10	↓	2.64-13.13 ng/ml (Adult male)				

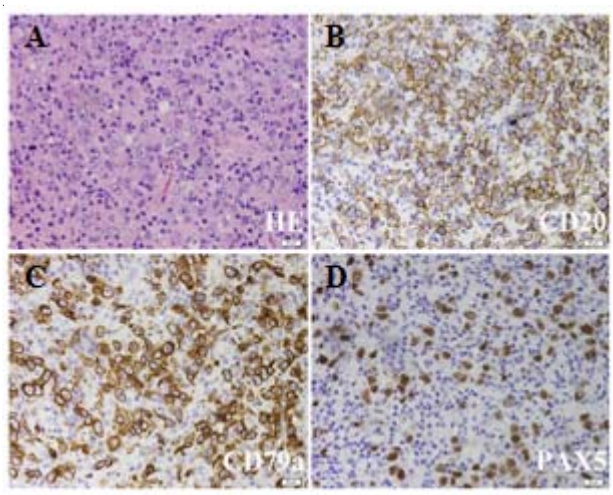

Figure 2. Tumor histopathology (× 400). **A:** The tumor consisted of large, round cells with abundant cytoplasm and polymorphic nuclei (H&E staining). **B:** Membranes are diffusely immunopositive for CD20, indicating a B-cell origin. **C:** Cytoplasm was strongly immunopositive for CD79a, validating a B-cell origin. **D:** Nuclei were scattered immunopositive for PAX5, confirming a B-cell origin.

Discussion

PCNSL, a rare form of extranodal non-Hodgkin's lymphoma [1], accounts for 0.8-1.5% to 6.6% of all primary CNS tumors [3]. Although PCNSL occurs more frequently in immunocompromised patients, the incidence has also increased in immunocompetent patients [2]. PCNSL has a predilection for the cerebral hemispheres, basal ganglia, corpus callosum, and periventricle [3]. Pure PCNSL involving the hypophysial fossa in immunocompetent patients without involvement of the brain parenchyma is very rare [6]. In one case, primary lymphoma, involving the pituitary stalk, presented with hydrocephalus and hyponatremia [8]. In another, primary lymphoma involving the bilateral hypothalamus presented with panhypopituitarism and diabetes insipidus [11]. In a third, primary lymphoma involving pituitary gland mimicked pituitary apoplexy [12]. In a fourth case, primary lymphoma involving the pituitary gland presented as hypophysitis [7]. To our knowledge, ours is the first report of PCNSL involving the hypothalamus, pituitary stalk, and pituitary gland simultaneously, with a dumbbell-shaped image. The normal host patient presented with DI and hypopituitarism. This is extremely rare and clinicians should consider the possibility of PCNSL when they see a nonspecific clinical presentation with an atypical sellar mass in neuroimaging.

With clinical manifestations, imaging findings, pituitary hormone levels, and final histopathological results, typical sellar masses are readily identified. However, atypical cases can be very puzzling initially.

Although pituitary adenomas account for more than 50% of sellar masses, other non-pituitary etiologies should be considered in the differential diagnosis, including tumorous lesions (e.g., craniopharyngioma, tuberculum sellae meningioma) and nontumorous lesions (e.g., hypophysitis, Rathke's cysts) [4]. Pituitary adenomas typically have symptoms suggesting anterior pituitary hyperfunction. They always grow upward to form spherical, slow-growing lesions in the saddle area with some degree of sella bone destruction. Non-pituitary etiologies are more likely to present with DI and cranial neuropathies. The presence of headache, visual compromise, or panhypopituitarism was reportedly not helpful in distinguishing a pituitary from a secondary non-pituitary etiology [10]. Our patient's initial presentation manifested as progressive DI and subsequent headache rather than disturbance of vision or the visual field. Hypopituitarism and hyperprolactinemia from stalk compression suggested encroachment on the anterior pituitary gland and stalk. The MRI characteristics included a homogeneously enhancing dumbbell-shaped lesion invading the hypothalamus, infundibulum, pituitary stalk, and gland, growth along the pituitary stalk, instead of upward, and the sella was intact. A pituitary adenoma was first excluded, and lymphocytic hypophysitis was suspected [13]. However, PCNSL was finally confirmed by a histopathological report and thorough examinations by CT, ultrasound, and PET. Variable presentations may delay accurate diagnosis and a stereotactic biopsy may be the best diagnostic strategy for this tumor [1].

From a review of the anatomy of the hypothalamus and pituitary, we noticed that the hypothalamus and posterior pituitary are directly supplied by branches of the systemic circulation, while the anterior pituitary is relatively protected by the sealed circulation of the portal venous system [9], so it seems reasonable to suppose that the hypothalamus and posterior pituitary may be particularly susceptible sites for primary or metastatic non-pituitary etiologies in the hypothalamic-pituitary axis. In a review of our patient, with a normal sella turcica and irregularly dumbbell-shaped sellar mass, we also suggest that this PCNSL originated from the hypothalamus and grew downward along the pituitary stalk to the pituitary fossa with no apparent destruction of the sella turcica.

Although PCNSL is a potentially curable primary brain tumor in the immunocompetent patient, the best treatment strategy has yet to be defined [1]. Current treatment options include biopsy followed by corticosteroids, radiation therapy, and chemotherapy. Most PCNSLs respond to corticosteroid treatment sensitively, but will relapse quickly when a corticosteroid is used alone. Whole-brain radiation therapy (WBRT) alone does not produce durable remissions, but it is usually combined with chemotherapy as a consolidation therapy, though we should be aware of treatment-related neurotoxicity, especially in elderly patients [5]. Our patient was finally diagnosed by biopsy. He responded well and durably to the initial chemotherapy (6 cycles of a high-dose methotrexate-based regimen) and subsequent WBRT (1 cycle). Today, he is in complete resolution in terms of clinical appearance and MRI imaging, and this has been documented for 11 months since surgery.

Conclusions

To our knowledge, this is the first reported case of a dumbbell-shaped PCNSL involving the hypothalamus, pituitary stalk, and pituitary gland simultaneously. The patient presented as DI and hypopituitarism in an adult immunocompetent subject. We suggest that the lesion originated from the hypothalamus and grew downward to the pituitary fossa along the pituitary stalk. Clinicians should consider the possibility of PCNSL in non-specific clinical presentations with atypical sellar masses on neuroimaging. The best management strategy for this tumor is a stereotactic biopsy. In our case, in an immunocompetent patient with a newly diagnosed primary CNS lymphoma, high-dose methotrexate (MTX)-based chemotherapy with whole-brain radiotherapy resulted in an excellent outcome.

The authors have no conflict of interest to report.

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