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CASE REPORT

A Biphasic Presentation of Diffuse Large B-cell Lymphoma Metastasis to the Hypothalamus-pituitary Axis: A Case Report and Literature Review

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Abstract

The Hypothalamus-Pituitary axis (HPA) is a rare location for metastasis of non-Hodgkin's lymphoma. Lymphomas constitute less than 0.5% of reported HPA metastasis. This case is unique in that, in addition to the noted panhypopituitarism; initial diagnostics demonstrated marked hyponatremia, consistent with syndrome of inappropriate antidiuretic hormone (SIADH), which was subsequently complicated by sudden diabetes insipidus (DI), suggesting hypothalamic/stalk infiltration. Despite low sensitivity, CSF cytology/flow cytometry may serve as a less invasive diagnostic measure. Treatment includes systemic chemotherapy with agents that cross the blood−brain barrier. Surgical resection alone or associated radiotherapy did not show an increase in survival. The prognosis remains poor.

Keywords: Pituitary metastasis, Hypothalamic pituitary axis, Non Hodgkin's lymphoma, Diffuse large B-cell lymphoma, Diabetes insipidus, DLBCL, SIADH

1. Introduction

Central nervous system (CNS) involvement is an unusual complication of non-Hodgkin's lymphoma (NHL); it more frequently affects the meninges or the peripheral cranial and spinal nerves.[1] The Hypothalamus-Pituitary axis (HPA) is a rare location for metastasis, with few cases reported in the literature (Table 1). These presentations may be clinically silent, manifest with visual issues due to the proximity to the optic chiasm, or present with a spectrum of symptoms ranging from isolated or complete anterior or posterior pituitary deficits to panhypopituitarism. Posterior pituitary deficits comprise almost 60% of reported cases, the majority manifesting as central DI.[2] Panhypopituitarism with DI is exceedingly rare, and a high level of clinical suspicion is critical. Management focuses on hormonal replacement and timely oncologic therapy. Notwithstanding, survival rates for NHL with CNS involvement remain extremely poor.[3]

2. Case description

A 57-year-old woman presented to the emergency department endorsing one day of severe, constant fatigue, nausea, and anorexia. Her symptoms started acutely, limiting her ability to function independently. She denied any associated symptoms, including polyuria, polydipsia, headache, or visual symptoms. She reported a medical history notable for Stage IIIB diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) without evidence of genetic rearrangements, diagnosed seven months before presentation. Her tumor was noted to be positive for MYC/BCL-2 expression on immunohistochemistry. She completed six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R−CHOP) three months before her current presentation, with complete resolution of previous metabolically active nodes on initial PET-CT. Unfortunately, two months before presentation she endorsed persistent lower back pain

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Table 1. Main clinical and radiologic features of secondary pituitary lymphoma reported in literature.

Reference	Type of Lymphoma	Clinical Features	Radiologic Findings
Leedman 1989[26]	Lymphomatous granulomatosis.	DI and hypogonadism.	HRCT with contrast: Pituitary stalk thickening predominantly at hypothalamic end.
Jonkhoff 1993[27]	Testicular NHL	Panhypopituitarism	CT scan with contrast: Large hypophyseal tumor with lateral infiltration around carotid arteries and cavernous sinus.
Ramsahoye 1996[28]	Angiocentric T-cell lymphoma.	DI	Brain MRI: Absence of normal signal from posterior pituitary. Otherwise, unremarkable.
Bushunow 1996[29]	Lymphomatous granulomatosis	DI	Brain MRI: Thickening hypophyseal stalk and empty sella appearance.
Shanks 1997[30]	High-grade B-cell lymphoma	None	Post-mortem finding.
Li 1998[31]	DLBCL	Panhypopituitarism	Brain MRI: Pituitary mass involving anterior and posterior pituitary.
Merlo 1999[32]	High-grade NHL	DI	Brain MRI: Enlarged, heterogenous hypophysis with enlargement of hypophyseal pedunculus.
Breidert 2000[33]	B-cell lymphoma	DI	Brain MRI: Thickening of pituitary stalk and infiltration of neurohypophysis.
Mathiasen 2000[34]	DLBCL	Hypothyroidism and central hypogonadism	Brain. MRI: Diffuse enlargement of pituitary gland, pituitary stalk at midline, enlargement bowed up the diaphragm.
Watabe 2000[35]	Angiotropic B-cell Lymphoma	Hyponatremia (SIADH), hypoglycemia	Post-mortem diagnosis.
Buchler 2002[36]	DLBCL	Panhypopituitarism and hyperprolactinemia	Brain MRI: Enhancement of pituitary gland and stalk. , increase size pituitary, stalk deviated to left.
Olgivie 2005[37]	DLBCL	Hypogonadism, hypothyroidism, hyperprolactinemia.	Brain MRI: Mass lesion wrapping itself around carotid arteries and peri-pituitary area.
Olgivie 2005[37]	T cell rich B- cell lymphoma	DI	Brain MRI: pituitary loss of the pituitary 'bright spot'
Jain 2008[38]	Hairy cell Lymphoma	Hypothyroidism and hyperprolactinemia	Brain MRI: Sellar mass with involvement in suprasellar regions. T2 bright and contrast enhancement.
Tamer 2009[39]	High-grade NHL	DI, Hypogonadisms and hyperprolactinemia	Brain MRI: Sellar mass involving pituitary gland, infundibular stalk, right cavernous sinus, sphenoid sinus, and right cranial nerves II, III, IV, V, VI.
Yang 2013[9]	Lymphatic plasma cell lymphoma	DI	Brain MRI: Small nodular lesion on hypothalamus and disappearance of normal high signal from the posterior pituitary.
Yang 2013[9]	Burkkit lymphoma	DI	Brain MRI: Small hypophyseal fossa with disappearance of high signals of the posterior fossa.
Akkas 2013[40]	DLBCL	None	CT-PET brain: Increase PET scan ^{8}F-FDG uptake with SUV_{max} of 45.06 in the pituitary.
Koiso 2014[41]	DLBCL	DI	Brain MRI: intra- and parasellar mass lesion extending to the upper clivus, sphenoid sinus, and right cavernous sinus.
Jaiswal 2019[42]	DLBCL	Panhypopituitarism	Brain MRI: Sellar mass extending into the suprasellar cistern into cavernous sinus.
Javanbakht 2018[10]	DLBCL	Panhypopituitarism with visual deficit	None available.
Wang 2016[43]	Mantle cell lymphoma	6th CN palsy and hypothyroidism	Brain MRI: Pituitary lesions involving cavernous sinuses bilaterally, no involving optic chiasma but abutting optic nerves.
Ravnik 2016[44]	DLBCL	Panhypopituitarism and DI	Brain MRI: Pituitary mass spreading in suprasellar space and compressing optic chiasma.

with associated paresthesia of the left lower extremity for which repeat PET-CT revealed a new hyperactive focus in the spinal canal at L2-L3, and an MRI was recommended. No lumbar puncture was performed at that time. MRI lumbar spine demonstrated an enhancing soft tissue mass that filled the spinal canal at the L2-L3 level as well as enhancement of the cauda equina nerve roots suggestive of metastatic disease. She received a short dexamethasone taper and sixteen cycles of

radiation therapy two weeks before her current presentation with subsequent resolution of her lower back pain and paresthesia. Four days following completion of radiation therapy (ten days before her sentinel presentation to our emergency department), she presented to an outside emergency department in the setting of generalized weakness, fatigue, nausea, and poor appetite. Laboratory diagnostics at that time revealed hyponatremia (125 meq/L), presumed to be hypotonic, hypovolemic hyponatremia for which she received IV crystalloid and was discharged with symptomatic resolution and an improved serum sodium (130 meq/L). She noted no baseline history of additional medication or illicit substance use.

On subsequent presentation to our emergency department four days later, she remained hemodynamically stable. Physical examination revealed no signs of dehydration or skin hyperpigmentation, nor evidence of visual field defects, abdominal tenderness, or peripheral edema. Laboratory diagnostics revealed a severe hypotonic hyponatremia (serum sodium 119 mmol/L (reference range: 135–148 mmol/L); serum osmolality 250 mOsm/kg (reference range: 275–295 mOsm/kg)). Elevated urine osmolality (461 mOsm/kg, reference range 50–1200 mOsm/kg) and a relatively elevated urine sodium (110 mmol/L, reference range 28–272 mmol/L), suggestive of SIADH with associated urinary salt wasting. Initial diagnostic imaging included a CT head that demonstrated thickening of the paramedian hypothalamic structures along the superior aspect of the dorsum sella and the adjacent superior portion of the pituitary infundibulum, which in conjunction with the noted hyponatremia, prompted additional biochemical workup for pituitary hormone abnormalities (Table 2). The workup demonstrated evidence of panhypopituitarism for which the patient was started on hydrocortisone 20 mg AM and 10 mg PM and levothyroxine 100 mcg PO daily.

Table 2. Laboratory diagnostics on admission.

Hormone	Reference Range	Value
Thyroid Stimulating Hormone	0.50–4.5	0.10 uIU/mL
Free T4	0.8–1.8	0.8 ng/dL
Luteinizing Hormone	10.0–54.7[a]	<0.3 mIU/mL
Follicle Stimulating Hormone	23.0–116.3	1.4 mIU/m
Adrenocorticotropic Hormone	6–50	>5 pg/mL
AM Cortisol	NA	1.3 mcg/dL
Cortisol Pre-Stim	NA	2 mcg/dL
Cortisol, 30′ Post	NA	12 mcg/dL
Cortisol, 60′ Post	NA	15.4 mcg/dL
Insulin-like Growth Factor	50–317	84 ng/mL

[a] Post-menopausal reference range.

Additional diagnostic workup included a pituitary MRI which demonstrated a partially empty sella with marked thickening and enhancement of the infundibulum with restricted diffusion, as well as T2/FLAIR hyperintensity and thickening of the bilateral hypothalamic, prechiasmatic optic nerves, chiasm, and optic tract, suspicious for metastatic lymphoma to the pituitary (Fig. 1). Given the noted CNS involvement, a lumbar puncture was performed and demonstrated a lymphocytic/monocytic pleocytosis (lymphocytes, 28/cu mm; monocytes, 48/cu mm) with marked elevation of cerebrospinal fluid (CSF) protein (159 mg/dL). CSF flow cytometry revealed a 6.2% phenotypically abnormal monoclonal B-cell, lambda positive phenotype consistent with the patient's known diffuse large B cell lymphoma.

Over the ensuing hospital days, the patient's serum sodium was corrected with continued medical therapy, and she was ultimately transferred to the Oncology service for induction. Unfortunately, routine labs before induction demonstrated a marked, rapid increase in the serum sodium from 136 meq/ml to 157 meq/L, which was associated with massive polyuria (1.1 L of urine in under 2 h) and an associated markedly low urine-specific gravity (1.003). She noted associated extreme fatigue, nausea, and vomiting with associated hypotension refractory to 2 L of crystalloid. The patient was diagnosed with Diabetes Insipidus (DI) and was administered hydrocortisone 50 mg IV q6hr, and vasopressin 0.5 mcg SC one time, with the resolution of symptoms and normalization of her blood pressure, serum sodium, and urine specific gravity.

Three days later, the patient was initiated on methotrexate and leucovorin. However, her course was complicated by continued, intermittent episodes of diabetes insipidus, requiring desmopressin. The patient completed one cycle of chemotherapy as an inpatient and was eventually discharged on desmopressin 0.1 mg BID, hydrocortisone 10 mg AM and 5 mg PM, and levothyroxine 100 mcg daily. Unfortunately, two weeks later, the patient was readmitted with acute onset of diplopia, frontotemporal headaches, nausea and vomiting, and intermittent urinary and bowel incontinence, with associated generalized weakness. MRI brain and spine revealed interval enlargement and thickening with signal abnormality in the pituitary stalk, cisternal optic nerves bilaterally, and chiasm with extension into the optic radiations, hypothalamus, in addition to the pituitary. Greater extension on FLAIR imaging into the post-chiasmal tracts and temporal radiations was also appreciated (Fig. 2). A similarly enhancing soft tissue within the

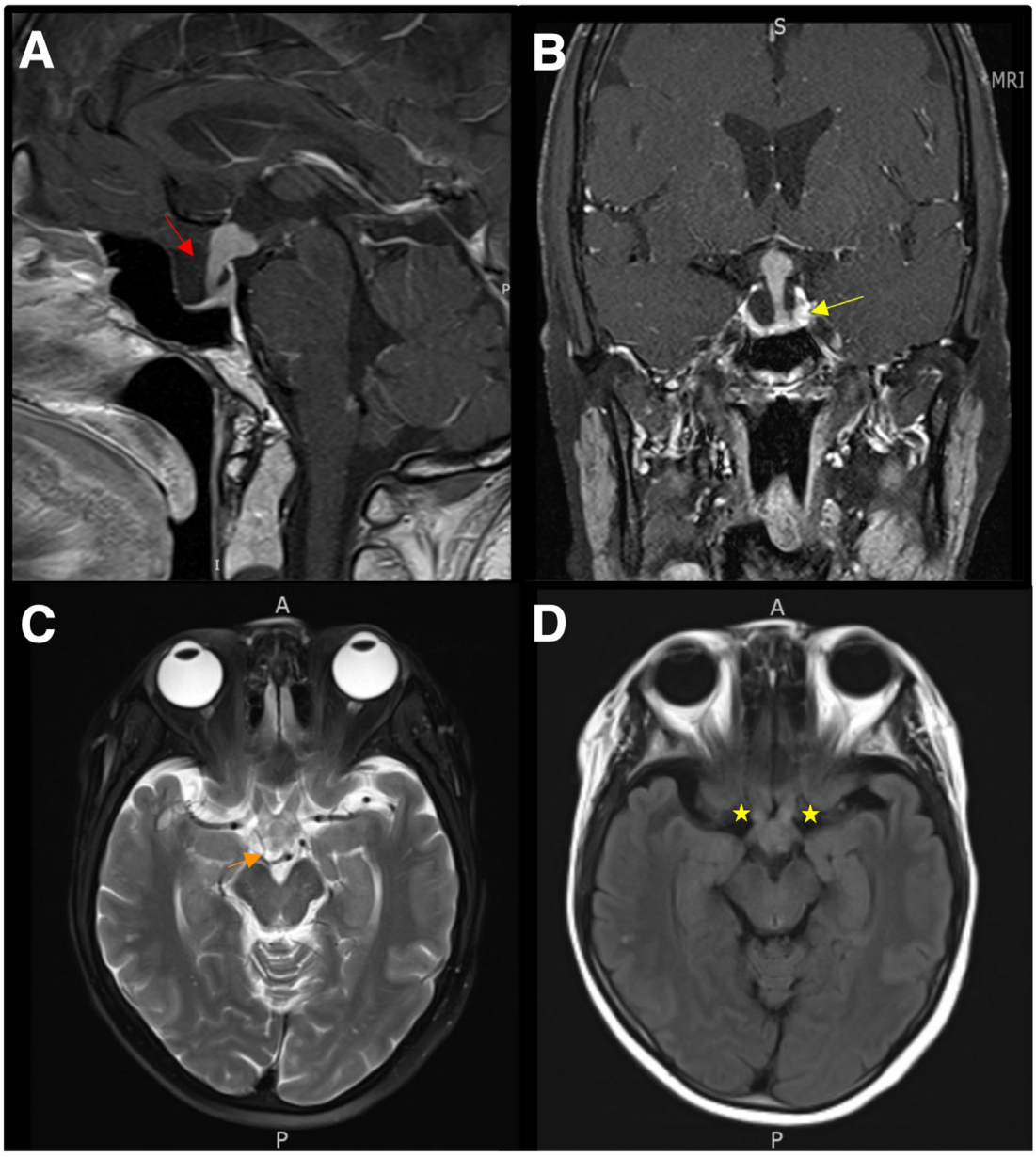

Fig. 1. Pituitary Magnetic Resonance Imaging with and without Contrast. T1 post-contrast sequences (Panels A, B) demonstrate a partially empty sella (Red arrow, A) lateral displacement of pituitary tissue (Yellow arrow, B). T2/FLAIR sequences (Panel C, D) demonstrate hyperintensity and thickening of the bilateral hypothalamic (Orange arrow, C), pre-chiasmic region, optic nerves, and optic tracts (Yellow stars, D).

lumbar spinal canal at the L2-L3 level with enhancement along the cauda equina nerve root was noted, consistent with the progression of metastatic DLBCL despite high dose methotrexate chemotherapy. Unfortunately, the patient passed away one month later.

3. Discussion

Brain metastases represent the most common tumors affecting the CNS,[4] yet the HPA remains an uncommon site of metastasis. The incidence of HPA metastasis varies, ranging from 0.14 to 4%[4–7] given the heterogenicity of the study samples – post-mortem analyses versus diagnostic radiology. Breast and lung cancer are the top culprits behind HPA metastasis, making up nearly 60% of cases,[7,8] compared to just 0.5% for lymphomas.[9] To our knowledge only twenty-four cases of metastatic lymphoma to HPA have been reported (Table 1); approximately 70% are NHL. Our patient represents an unprecedented case of metastatic DLBCL to the leptomeninges, hypothalamus, and pituitary infundibulum that presented in the context of associated

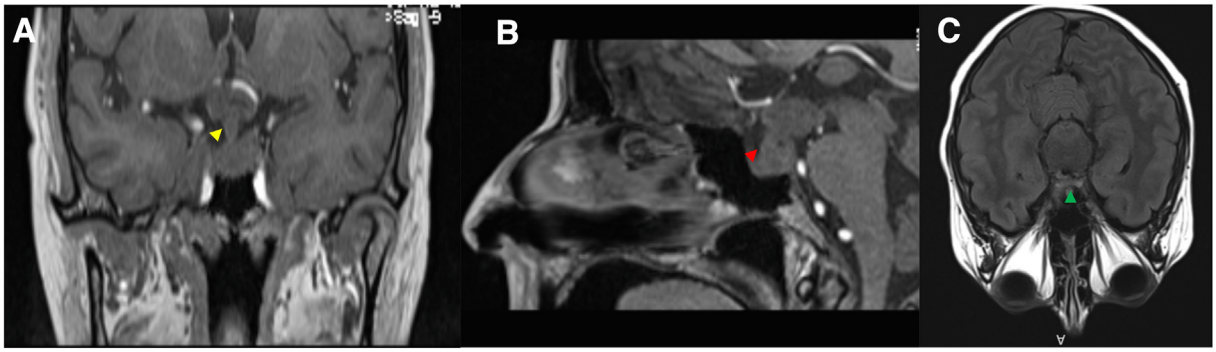

Fig. 2. Pituitary Magnetic Resonance Imaging without Contrast on Follow-Up. T1 sequences (Panels A, B) demonstrated interval enlargement and thickening with associated signal abnormality in the pituitary stalk (Yellow arrowhead, A), cisternal optic nerves, optic chiasm with extension into the optic radiations, hypothalamus, and pituitary (Red arrowhead, B). There is an associated extension into the right cavernous sinus and Meckel's cave. T2/FLAIR sequences (Panel C) demonstrate further extension into the post-chiasmal tracts and temporal, optic radiations (Green arrowhead, C).

panhypopituitarism that manifested initially as SIADH followed by sudden DI confirmed with the presence of malignant cells of CSF cytologic analysis.

The clinical manifestations of pituitary metastasis depend on the specific HPA or extrasellar areas involved. Javanbakht et al.[10] found that visual defects were the most common symptom reported in the literature from 1957 to 2018 (141/463, 48.4%), followed by DI (38.4%), and panhypopituitarism (37.7%). In cases of NHL metastases, the predominant manifestation is DI followed by panhypopituitarism, with predominant gonadotropic hormone deficits in most of the cases and more variable effects of other anterior pituitary hormones (Table 1). In our case, the sequence of endocrine manifestations was remarkable. The patient remained minimally symptomatic, with excellent tolerance to chemotherapy and radiotherapy before presentation. Based on this, we hypothesize that the HPA axis was intact up to a couple of weeks before presentation. This is supported by a normal ACTH stimulation test that suggested the absence of adrenal atrophy.[11] Interestingly, the main electrolyte abnormality in our patient was severe hyponatremia, initially attributed to hypovolemia due to response to crystalloid therapy at outside hospital, with a marked worsening on presentation to our facility. NHL CNS metastasis, hypothyroidism, and glucocorticoid deficiency are common causes of SIADH. Each one of these diagnostic findings was present in our patient. Glucocorticoid deficiency can contribute to hyponatremia via a dual mechanism: impaired renal water excretion and non-osmotic secretion of ADH.[12] Hyponatremia caused by hypothyroidism is considered uncommon and usually occurs in severe hypothyroidism with myxedema. In severe myxedema, decreased cardiac output stimulating ADH release via the carotid sinus baroreceptors is postulated to contribute to hyponatremia.[13] In patients with coexisting hypothyroidism and hypopituitarism, the contribution of hypothyroidism to hyponatremia is likely minimal.[12] Central DI results from various processes that result in a decrease in either hypothalamic production or posterior pituitary storage of ADH. Moreover, infiltrative causes may result in central DI by thickening the pituitary infundibulum (reduced transport of ADH to the posterior pituitary). In a majority of cases, central DI with infundibular thickening is associated with anterior pituitary deficiencies.[14] Intriguingly, the plateau hyponatremia despite glucocorticoid and thyroid supplementation and sudden development of DI within days may suggest a biphasic response in the setting of hypothalamic/stalk infiltration impacting the neurosecretory pathway. To our knowledge, this phenomenon has not been previously described in pituitary metastasis.

Posterior pituitary metastases are common, likely due to the rich vascular supply arising directly from the carotid system via hypophyseal arteries,[15] however, the anterior lobe can be equally affected.[16] Other proposed mechanisms of HPA metastases include contiguous spread from the base of the skull[17] or suprasellar cistern from leptomeningeal spread.[18] Given the positive findings on CSF cytology, we suspect the latter is the main mechanism of metastasis in our patient. In regards to histologic patterns of the spread of HPA metastasis, a recent study from Kleinschmidt-DeMasters et al.[19] demonstrated that capsular involvement is the most common pattern (46%) followed by posterior gland infiltration (36%). In this series, two metastatic lymphomas were found in autopsy specimens (mantle cell lymphoma and a small bowel lymphoma) and in

both cases, focal capsular infiltrates were found without obliteration or infiltration of the anterior or posterior pituitary.[19] In our patient, tissue biopsy was not necessary based on the antecedent of stage IV DLBCL and positive CSF cytology.

In most cases, the diagnosis of NHL precedes or is made simultaneously with pituitary metastasis; therefore, imaging and cytology become crucial for distinguishing metastatic lesions from other pituitary pathologies.[9] MRI with and without contrast of the pituitary is more sensitive than CT for the characterization of malignant infiltration.[9] Although there are no pathognomonic radiologic findings, the presence of bone destruction, infiltration, or an asymmetric, lobular, and/or dumbbell-shaped expansion into the suprasellar region are suggestive findings of metastatic disease.[20] In some reported cases of metastatic NHL, low T1WI and T2WI signals of the pituitary gland are common signs (Table 1). The basis of these radiologic findings lies in the fact that posterior lobe, in normal circumstances, exhibits hyperintensity on T1WI due to a continuous outflow of ADH and oxytocin from the hypothalamic neurons through the capillaries for storage.[21] Therefore, the disappearance of normal enhancement of the posterior pituitary will be seen in the presence of infiltrative lesions in the hypothalamus, pituitary stalk, or neurohypophysis, especially if DI is present.[9] Other imaging modalities including PET-CT scan may reveal an increased uptake of 18 F-FDG PET in the presence of pituitary metastasis,[22,23] however, given the overall increase in CNS uptake at baseline it may not be as sensitive as MRI for detection of pituitary metastases. Pathological confirmation is required in cases of clinical uncertainty or unclear radiologic findings. For CNS lymphomas (primary or secondary), CSF analysis by conventional cytology and flow cytometry provides high specificity but low sensitivity.[24] Many other reported cases required intracranial biopsies or excisional biopsies via Endoscopic Endonasal Approach (EEA) (Table 1). To our knowledge, the case presented in this report is the only patient with DLBCL with pituitary metastasis and positive CSF cytologic analysis.

Treatment options usually include systemic chemotherapy with agents that cross the blood–brain barrier, commonly a methotrexate-containing regimen. Radiotherapy is reserved for cases of therapeutic failure or severe disease. Resection by EEA alone or associated radiotherapy did not show an increase in survival.[25] Unfortunately, the prognosis is poor, with a mean survival of 13.6 months.[10] In our case, the patient survived only 2 months following the diagnosis of DLBCL metastasis to the HPA, with progression of her disease despite one cycle of high-dose methotrexate chemotherapy.

4. Conclusion

In conclusion, the pituitary gland is an extremely uncommon site for CNS metastasis; metastatic lymphoma in this area is even rarer. The presence of ophthalmoplegia or other visual disturbances and/or signs of pituitary hormonal deficits, particularly DI should raise suspicion in those with a pre-existing oncologic history. MRI with and without contrast is the most accurate non-invasive diagnostic modality. Despite low sensitivity, CSF cytology/flow cytometry may provide an alternative, less invasive technique, to evaluate for metastasis in unclear cases.

Ethics information

The abstract was presented at the Endocrine Society 2023 annual meeting in Chicago, Illinois.

Disclaimers

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Conflict of interest

All authors declare no conflict of interest.

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