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**Case Report**

# Pituitary Infiltration by Lymphoma

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## Abstract

Lymphoma infiltration to the pituitary is rare. It represents less than 0.5% of all reported pituitary metastases (PMs). Here we present a case series of 3 patients with PMs from a systemic lymphoma. Also, we performed a literature review of the cases reported. We identified additional 31 cases in which non-Hodgkin lymphoma (NHL) was the most common (n = 28, 90%), with large B-cell NHL the most frequent histological subtype (n = 14, 45%). Central hypothyroidism (n = 21, 67%) was the most frequent pituitary deficiency followed by adrenal insufficiency (n = 19, 61%) and diabetes insipidus (DI; n = 18, 58%). Full endocrine recovery was found in only 12% (n = 4) of patients after treatment, and magnetic resonance imaging showed tumor regression in 22% of them. In our series, 2 patients were diagnosed with diffuse large B-cell lymphoma, and 1 had mixed cellularity of classic Hodgkin lymphoma. The mean age was 54 ± 6.92 years. Hypopituitarism and DI were present in all of them, with 100% of mortality because of advanced systemic disease.

**Key Words:** cancer, anterior pituitary, infiltrative disease, hypopituitarism

**Abbreviations:** AI, adrenal insufficiency; CT, computed tomography; DI, diabetes insipidus; HL, Hodgkin lymphoma; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; PET, positron emission tomography; PM, pituitary metastasis.

Pituitary metastases (PMs) are rare, representing only 1% of all operated pituitary tumors, and 0.4% of all metastatic disease [1]. The first case of PMs was described in 1857, in a patient with pituitary infiltration from a metastatic melanoma [2]. Currently, breast and lung cancer are the most common neoplasia causing 60% of PMs, followed by kidney, prostate, and colon cancer, with a prevalence between 3% and 5%. Pituitary infiltration by hematologic malignancies is even rarer [3], and systemic lymphoma is the main cause representing 0.5% of them [4].

PMs can involve both the anterior and posterior gland. Diabetes insipidus (DI) is a common clinical presentation when the posterior lobe is affected. Hypothyroidism and central adrenal insufficiency (AI) are the 2 main anterior pituitary hormone deficiencies. Other associated symptoms include headache, visual field defects, ophthalmoplegia, fatigue, weight loss, nausea, and vomiting [3, 5].

Here we analyzed information of 31 cases previously reported, and we describe 3 new cases of patients with Hodgkin (HL; n = 1) and non-Hodgkin lymphoma (NHL; n = 2) that metastasized to the pituitary gland.

## Case 1

A previously healthy 60-year-old woman presented to our hospital with a 12-month history of headache, drowsiness, excessive thirst (with water intake up to 5 L/day), nausea, and vomiting. A complete visual loss of the right eye, and decreased visual acuity in the left one, caused her to seek medical attention.

Initial evaluation revealed severe hypernatremia (185 mEq/L), high serum osmolarity (374 mOsm/kg), low urine density (1.005 g/mL), and low urine osmolarity (172 mOsm/kg). Brain magnetic resonance imaging (MRI) showed a sellar, hypothalamic, and skull base infiltration with intraorbital extension. The pituitary gland was slightly enlarged with a heterogeneous and enlarged infundibulum. The neurohypophysis shows its characteristic bright spot (Fig. 1). DI was diagnosed and desmopressin therapy was started with good tolerance and symptom improvement. Central hypothyroidism, hypogonadism, and hypocortisolism, along with moderate hyperprolactinemia, was diagnosed after anterior pituitary evaluation (Table 1). Levothyroxine and hydrocortisone were started and well tolerated.

Positron emission tomography (PET) scan showed hypermetabolic lesions with diffuse metabolism (SUVmax 9.2) on the hypothalamus, with bilateral intraorbital tissue, and enlarged cervical and external iliac lymph nodes.

A biopsy from inguinal adenopathy confirmed diffuse large B-cell lymphoma (CD20+, CD3−, cyclin D1−, BCL2+, and Ki-67 index < 10%) infiltration. The patient died of chemotherapy-related side effects a few weeks later.

## Case 2

A 44-year-old man had a positive history of HIV, chronic hepatitis B infection, and a diffuse large B-cell lymphoma (CD20+, CD3−, CD 10+ > 30%, BCL6−, MUM1− < 20%, CD30−, CD138−, LMP1−, HHV8−, BCL2+ > 30%, and

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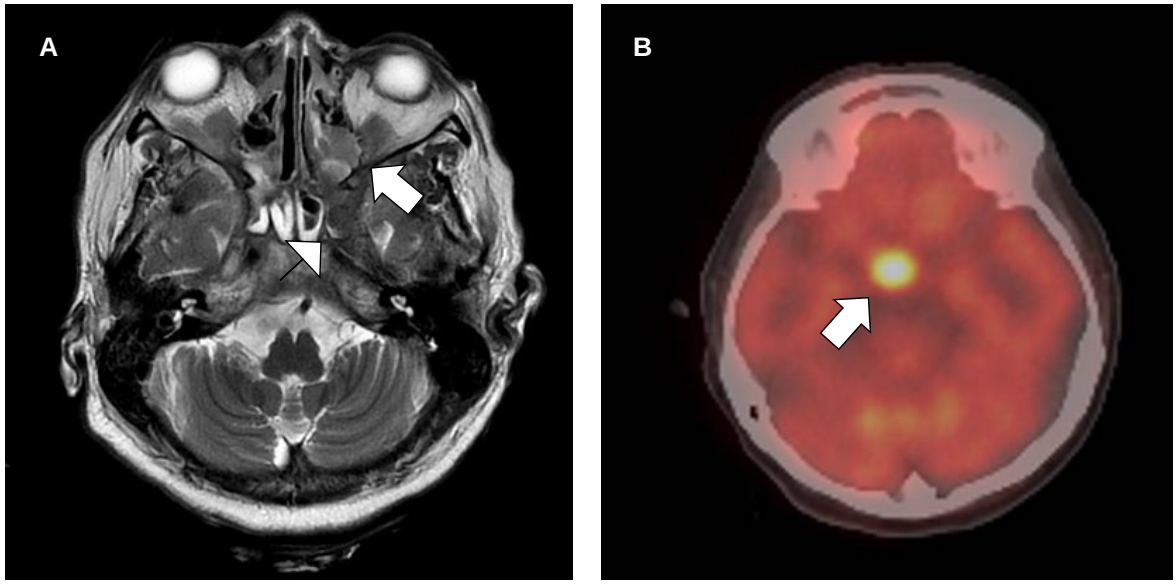


**Figure 1.** A, Magnetic resonance imaging of case 1 with sellar, hypothalamic, and skull base infiltration of non-Hodgkin lymphoma (arrowhead) with intraorbital extension (arrow). B, F-FDG positron emission tomography/computed tomography showing a hypermetabolic hypothalamic lesion.

KI-67 60%). He received chemotherapy with DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), and then rituximab, methotrexate, and cytarabine. After 10 months, the patient began experiencing diffuse headaches and generalized tonic–clonic seizures. During hospitalization, polydipsia and polyuria syndrome (~5 L/day) were documented, and together with hypernatremia (158 mEq/L), high serum osmolarity (325 mOsm/kg), low urine density (1.003 g/mL), and a urine osmolarity of 204 mOsm/kg, central insipidus diabetes were confirmed. An MRI scan reported a heterogeneous enhancement of the anterior pituitary without focal lesion and absence of posterior pituitary hyperintensity on T1, with intra-axial, supratentorial, and infratentorial leptomeningeal tumor infiltration.

Anterior pituitary function evaluation confirmed central hypothyroidism and AI (see Table 1). Intranasal desmopressin, levothyroxine, and hydrocortisone were started. Since the systemic clinical syndrome related to the lymphoma recurrence started together with the hypopituitarism and DI, it was attributed to pituitary infiltration. During hospitalization, neurological worsening was documented with Parinaud syndrome, an incomplete right pyramidal syndrome, and cerebellar dysfunction. Due to disease progression and spread to the central nervous system, the patient decided not to continue treatment and started palliative care, dying after 1 month.

## Case 3

A 50-year-old man was admitted to our institution because of chronic headache, visual and auditory hallucinations, left facial palsy, asthenia, anorexia, nocturnal diaphoresis, intermittent fever of up to 38 °C, and weight loss of 15 kg. A palpable lymphadenopathy was detected on physical exam, and confirmed with a computed tomography scan. Also, an MRI scan showed a tumoral lesion with pituitary infiltration, enlargement of the sella turcica, loss of the posterior lobe bright signal, homogeneous enhancement after gadolinium administration, bilateral cavernous sinus invasion, and extension to the suprasellar cistern and hypothalamic region (Fig. 2). A biopsy of the cervical lymph node was performed diagnosing classic HL with mixed cellularity. During hospital admission, hypernatremia (158 mEq/L), high serum osmolarity (310 mOsm/kg), low urine density (1.001 g/mL), and a urine osmolarity of 321 mOsm/kg were found, suggesting DI. After additional laboratory evaluation we confirmed central hypothyroidism, and hypogonadism, slight hyperprolactinemia, and low morning serum cortisol (see Table 1). Intranasal desmopressin, levothyroxine, and hydrocortisone were started. A transsphenoidal biopsy confirmed pituitary infiltration by HL (CD15+, CD30+, LMP1+, PAX5+, ALK−, CD20−). Ten sessions of 30-Gy radiotherapy were administered without complications. ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) was started. After 4 cycles, MRI scan revealed complete response with no tumor remnant (see Fig. 2). However, PET scan revealed systemic disease progression and additional chemotherapy with GDP (gemcitabine, dexamethasone, and cisplatin) was started. Unfortunately, the patient died soon after of septic shock.

## Discussion

Lymphoma infiltration to the pituitary gland is a quite rare condition [6]. Clinical presentation can be heterogeneous and, usually, affected cases have a poor prognosis. Therefore, it is important to recognize clinical and biochemical information to promptly identify and treat such cases. Information about metastatic lymphomas to the pituitary gland have usually been obtained from single case reports (Table 2) [6-17, 19-21, 23-33]. We reiterate here important information related to 3 confirmed cases of pituitary infiltration by lymphoma, and, additionally, we provide a literature review of 31 additional cases reported previously [4, 6-33]. These cases were identified after conducting database research of indexed articles at PubMed, Medline, EBSCO, Web of Science, ScienceDirect, Scopus, and OVID. The terms used were "*pituitary & lymphoma & metastases*" and "*pituitary & lymphoma & infiltration*" between 1975 and June 1,

**Table 1. Clinical and biochemical characteristics of cases reported at diagnosis**

| Variable | Case 1 | Case 2 | Case 3 | Normal values |
|---|---|---|---|---|
| Sex | F | M | M | — |
| Age, y | 60 | 44 | 50 | — |
| FSH, IU/L | 0.9 | 7.4 | 0.6 | 1.27-19.26 |
| LH, IU/L | 0.1 | 5.6 | 0.2 | 1.24-8.62 |
| Free T4, ng/dL | 0.6 | 0.5 | 0.4 | 0.63-1.34 |
| TSH, µU/mL | 0.05 | 0.5 | 11.6 | 0.03-5.00 |
| Cortisol, µg/dL | 4.0 | 4.1 | 0.8 | 6.7-22.6 |
| ACTH, pg/mL | 10 | 23 | — | 10-100 |
| Prolactin, ng/mL | 138 | — | 71 | 3.9-2.5 |
| Growth hormone, ng/mL | 0.17 | — | 0.48 | 0-13 |
| IGF-1, ng/mL | 54 | 83 | 49 | 44-241 |
| Testosterone, ng/mL | — | — | < 0.1 | 1.75-7.81 |
| Lymphoma subtype | Diffuse large B-cell non-Hodgkin lymphoma | Diffuse large B-cell non-Hodgkin lymphoma | Hodgkin lymphoma with mixed cellularity | — |
| Follow-up | Died of chemotherapy-related side effects | Died under palliative care | Died of septic shock | — |

Abbreviations: ACTH, adrenocorticotropin; F, female; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; M, male; T4, thyroxine; TSH, thyrotropin.

2022 (see Table 2). Results showed 31 patients with infiltration of lymphoma at the pituitary gland. Of these, NHL accounted for 90% of cases (n = 28, 90%), and HL the remaining 10% (n = 3). The most frequent NHL subtype was diffuse large B-cell lymphoma (45%, n = 14), a very aggressive neoplasm that commonly metastasizes to the central nervous system [34]. However, pituitary infiltration is seen in less than 1% of cases. The age of presentation ranged from 39 to 78 years in women and 19 to 77 years in men, with a 2:1 man (n = 20) to woman (n = 11) ratio, suggesting that pituitary infiltration is more common in men. In our series, 2 patients had diffuse large B-cell lymphoma and 1 had a classic HL with mixed cellularity (Fig. 3). Similarly, the age in our cases ranged from 44 to 60 years and was more common in men.

Pituitary involvement was the initial presentation of a systemic lymphoma in 58% of patients (n = 18) [4, 8, 13, 16, 18, 20-23, 25, 27-31, 33]. Also, a similar proportion of cases was identified throughout the disease activity (22%, n = 7) [9-11, 14, 15, 19, 24] or were a consequence of lymphoma recurrence (19%, n = 6) [6, 7, 12, 17, 26, 32]. Additionally, cases 1 and 3 presented here started with DI, and case 2 after recurrence of systemic disease.

Posterior pituitary invasion by tumor metastasis was reported more often than anterior lobe involvement [35]. This was attributed to the posterior lobe circulation coming

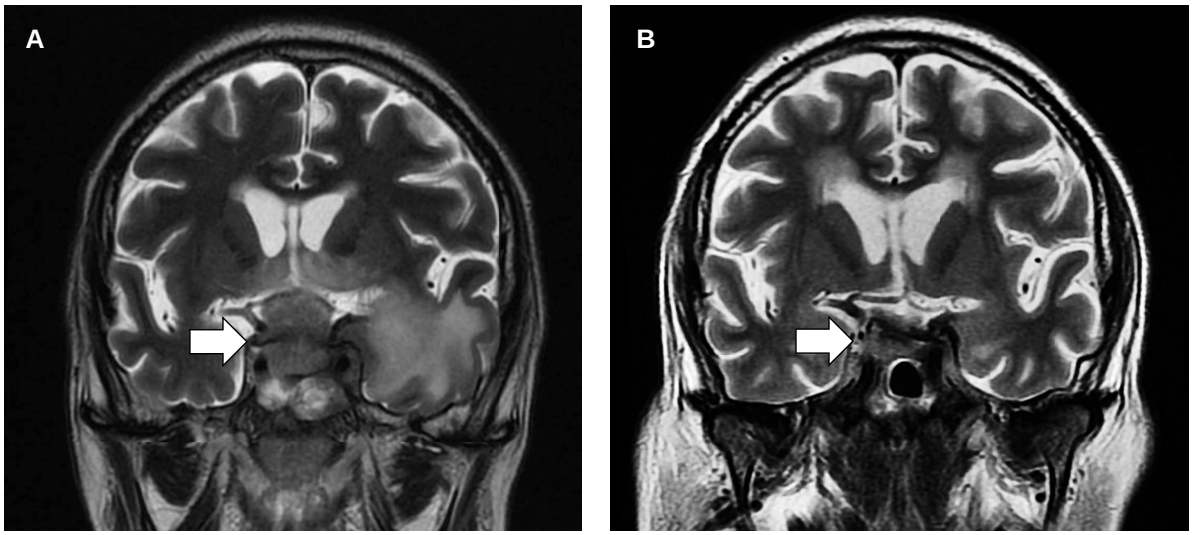


**Figure 2.** Coronal T2, contrast-enhanced sequence of the magnetic resonance imaging of case 3, showing tumor volume before (left, white arrow) and after (right, white arrow) chemotherapy.

**Table 2. Literature review of previously reported cases (n = 31)**

| No. | Reference/Y [ref] | Age/ Sex | Lymphoma type | Clinical features | Endocrinological features | MRI findings | Follow-up |
|---|---|---|---|---|---|---|---|
| 1 | Bunick/1978 [7] | 47/M | HL | Headache, diplopia, hearing loss, low libido, lethargy | HT, AI | None<br>Skull x-ray—destruction of floor of sella | Not reported |
| 2 | Leedman/1989 [8] | 19/M | NK-/T cell lymphoma | Polyuria/Polydipsia, fever | DI | None<br>CT—TPS | Died 18 mo after diagnosis |
| 3 | Jonkhoff/1993 [9] | 65/M | NHL | Oculomotor palsy, diplopia/ptosis, scrotal mass, fatigue | HT, AI, HG | Pituitary tumor around carotid arteries and cavernous sinus | CR, hypopituitarism persists |
| 4 | Ramsahoye/1996 [10] | 56/F | NK-/T-cell lymphoma | WL, fever, thirst, rash | HP, DI | ANSPP | Died of pneumonia 18 wk after diagnosis |
| 5 | Bushunow/1996 [11] | 50/M | NK-/T-cell lymphoma | Rash, fever, weakness, low back pain | DI | None<br>CT—TPS, empty sella | CR 6 y after treatment |
| 6 | Ashigbi/1997 [12] | 33/M | HL | Fever, 3rd nerve palsy | AI | Enhancing lesion in region of sella turcica | CR for 62 mo |
| 7 | Li/1998 [13] | 77/M | Diffuse large B-cell NHL | Weakness, confusion, polyuria | HT, AI | Pituitary mass | Died 9 wk after diagnosis |
| 8 | Merlo/1999 [14] | 64/M | B-cell NHL | Abdominal pain, polydipsia/polyuria | DI | DEPG | RMRI |
| 9 | Breidert/2000 [15] | 37/M | B-cell NHL | Facial pain, polyuria | DI | TPS | CR, ER |
| 10 | Mathiasen/2000 [16] | 65/M | Diffuse large B-cell NHL | Low libido, fatigue, weakness, dyspnea | HP, HT, AI, HG | DEPG | Not reported |
| 11 | Büchler/2002 [17] | 69/F | Diffuse large B-cell NHL | Weakness, fever, WL, polyuria/polydipsia, anasarca | HP, HT, AI, HG | DEPG | CR after 2nd cycle of CHOP |
| 12 | Ogilvie/2005 [18] | 59/M | Diffuse large B-cell NHL | Headache, ptosis, photophobia | HT, AI, HG | Leptomeningeal mass | CR for 18 m<br>Hypopituitarism persists |
| 13 | Ogilvie/2005 [18] | 53/M | Diffuse large B-cell NHL | Polyuria, WL, headache, night sweats | HG, DI | ANSPP | Lost to follow-up |
| 14 | Jain/2008 [19] | 41/M | T-cell lymphoma | Fever, headache, visual loss, polyuria | HP, HT | Sellar and suprasellar mass | Died 1.5 y after diagnosis |
| 15 | Tamer/2009 [20] | 70/F | B-cell NHL | Headache, fatigue, diplopia/ptosis | HP, HG, DI | Sellar mass | Died after biopsy |
| 16 | Kenchaiah and Hyer/2011 [21] | 65/F | Diffuse large B-cell NHL | Lethargy, appetite loss, edema | HP, HT, AI, HG | None<br>PET scan–pituitary involvement | CR, ER |
| 17 | Tan and Aguinaldo/2013 [6] | 57/M | Burkitt lymphoma | Fever, abdominal pain, polyuria/polydipsia | HP, HG, DI | ANSPP and TPS | Incomplete treatment DSS |
| 18 | Yang/2013 [4] | 20/M | LPL | Fever, WL, polyuria/ polydipsia | DI | HI, ANSPP | Incomplete response RMRI |
| 19 | Yang/2013 [4] | 26/M | Burkitt lymphoma | Polyuria/Polydipsia | DI | ANSPP and TPS | RMRI |
| 20 | Foo and Sobah/ 2014 [22] | 39/F | Burkitt lymphoma | Painful diplopia, ptosis, vomiting, WL, headache | HP, HT, AI, HG | DEPG, COC, thickened lateral walls of both cavernous sinuses | Incomplete treatment DSS |
| 21 | Valeros and Khoo/ 2014 [23] | 69/M | Diffuse large B-cell NHL | Dizziness, WL, strabismus, fever, postural hypotension | HT, AI, HG | Hypodensities in pituitary gland | DSS after 2 cycles of CTX |
| 22 | Koiso/2014 [24] | 78/F | Diffuse large B-cell NHL | Diplopia, ptosis, back pain, fever | DI | Sellar mass extending to sphenoid and cavernous sinus | CR 4 y after diagnosis |
| 23 | Kumabe/2015 [25] | 72/F | Diffuse large B-cell NHL | Anasarca | HT, HG | Swelling of pituitary gland | CR, ER |
| 24 | Wang/2016 [26] | 70/F | Mantle cell lymphoma | Headache, nausea/ vomiting<br>6th cranial palsy | HT | Enhancing sellar and suprasellar mass, COC | RMRI at 3 and 6 mo |

(*continued*)

**Table 2. Continued**

| No. | Reference/Y [ref] | Age/ Sex | Lymphoma type | Clinical features | Endocrinological features | MRI findings | Follow-up |
|---|---|---|---|---|---|---|---|
| 25 | Ravnik/2016 [27] | 60/M | Diffuse large B-cell NHL | Fatigue, WL, night sweats, abdominal pain, nausea/vomiting | HT, AI, HG, DI | Sellar and suprasellar mass and COC | RMRI at 3 y |
| 26 | León-Suárez/2016 [28] | 64/F | Diffuse large B-cell NHL | Dyspepsia, nausea/ vomiting thirst, fatigue, WL | HP, HT, AI, HG, DI | Pituitary enhancement, TPS, OC, and HPI | Reduction of TPS, DSS |
| 27 | Stegink/2019 [29] | 39/M | Diffuse large B-cell NHL | Massive gastrointestinal bleeding, polyuria | HT, AI, DI | TPS | No response to treatment |
| 28 | Jaiswal/2019 [30] | 42/F | Diffuse large B-cell NHL | Amenorrhea, headache, visual field reduction, fatigue, WL, limb pain | PH | Sellar and suprasellar mass. HPI | Died 2 mo after CTX initiation |
| 29 | Zahedi/2020 [31] | 64/F | Low-grade B-cell NHL | Diplopia, headache, proptosis, weakness, WL | HT, AI, DI | Sellar and suprasellar enhancement, TPS | CR, ER |
| 30 | Vega/2020 [32] | 69/M | Diffuse large B-cell NHL | Weakness, hypercalcemia, hypoglycemia | HP, HT, AI | TPS and DEPG | Died 5 d after diagnosis |
| 31 | Pineda-Galindo/ 2020 [33] | 31/M | NK-/T-cell lymphoma | Multiple cranial mononeuropathy | HP, HT, AI | Pituitary hyperintensity, sphenoid sinusitis | Died 10 mo after diagnosis |

Abbreviations: AI, adrenal insufficiency; ANSPP, absence of normal signal from posterior pituitary; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COC, compression of the optic chiasm; CR, complete response; CT, computed tomography; CTX, cyclophosphamide; DEPG, diffuse enlargement of the pituitary gland; DI, diabetes insipidus; DSS, died of septic shock; ER, endocrinology recovery; HG, hypogonadism; HL, Hodgkin lymphoma; HP, hyperprolactinemia; HPI, hypothalamus infiltration; HT, hypothyroidism; LPL, lymphoplasmacytic lymphoma; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; NK, natural killer; OC, optic chiasm; PET, positron emission tomography; PH, panhypopituitarism (unspecified pituitary axes); RMRI, reduction on magnetic resonance imaging scan; TPS, thickened pituitary stalk; WL, weight loss.

directly from the hypophyseal arteries, while the anterior lobe is nourished through the portal system [36]. However, in our case series and after literature review, we noticed that lymphoma may infiltrate more commonly the anterior (52%, n = 16) [7, 9, 12, 13, 16-20, 22, 23, 25, 26, 30, 32, 33] rather than the posterior (26%, n = 8) [4, 8, 10, 11, 14, 24] pituitary lobes. Interestingly, both lobes were affected in 22% of cases (n = 7) [6, 18, 20, 27-29, 31]. Similarly, our 3 patients had anterior and posterior involvement. Therefore, we observed that the anterior pituitary lobe was the most commonly affected, followed by infiltration of both pituitary lobes, the rarest being the posterior lobe infiltration. Since the main route of lymphoma metastasis may not be hematogenous, this may explain such pituitary infiltration distribution. Central hypothyroidism (67%, n = 21) was the most frequent hormonal deficiency [7, 9, 13, 16-19, 21-23, 25-33], followed by AI (61%, n = 19) [9, 12, 13, 16-18, 21-23, 27-31] and DI (58%, n = 18) [4, 6, 8, 10, 11, 14, 18, 20, 24, 27-29, 31] (Fig. 4). Hyperprolactinemia appeared in 2 of our patients, with levels of 139 ng/mL (case 1) and 71 ng/mL (case 2), which was attributed to pituitary stalk compression. Additional common symptomatology included fever, weight loss, and fatigue, as well as headache together with syndromes related to cranial nerve or optic chiasm compression [4, 6-33].

Although there are no specific radiological findings for pituitary infiltration by lymphomas, the most commonly reported

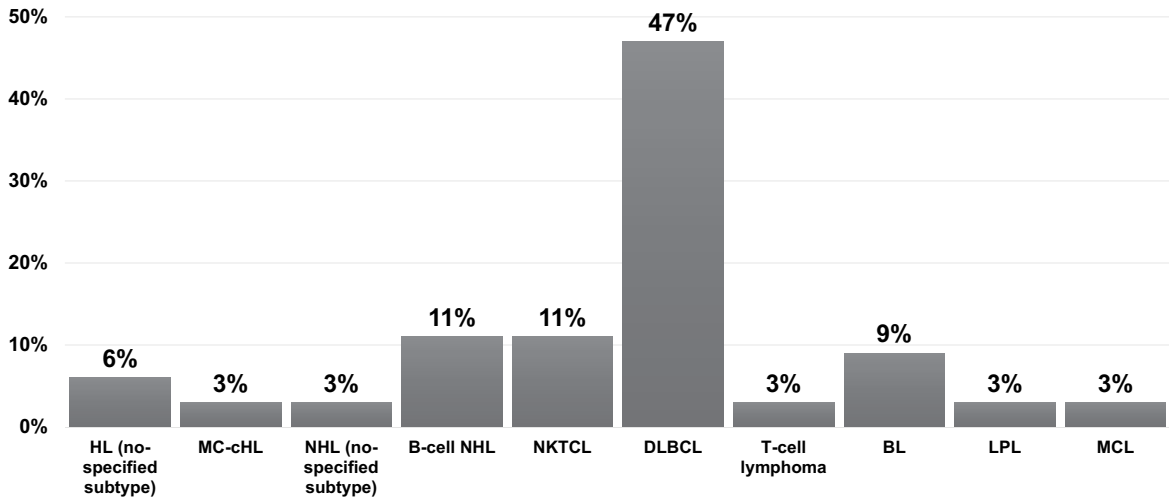


**Figure 3.** Histopathologic diagnosis of pituitary biopsy of the previously reported cases with systemic lymphoma (n = 31).

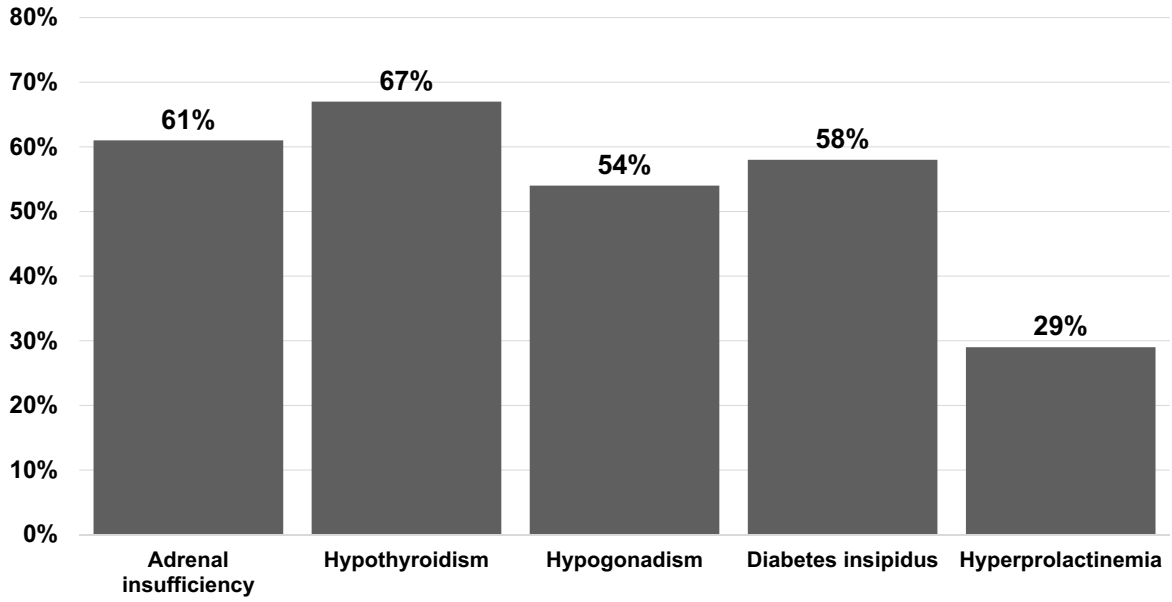


**Figure 4.** Hormonal abnormalities reported in patients with lymphoma pituitary infiltration (n = 34).

result was homogeneous enhancement after gadolinium administration, isointense on T1-weighted, and isointense to hypointense on T2-weighted images [24]. Cases 1 and 3 have images consistent with sellar and hypothalamic infiltration. Cases 2 and 3 showed absence of posterior pituitary lobe hyperintensity on simple T1 sequences, and in case 1 the bright spot was present.

Importantly, in patients with a confirmed systemic lymphoma diagnosis and MRI scan suggesting pituitary infiltration who started with hypopituitarism, pituitary biopsy is rarely necessary to confirm lymphoma infiltration [28]. Diagnosis can be confirmed after therapeutic response, since usually reduced pituitary tumor volume appears quickly after systemic chemotherapy, which is not common in other pituitary diseases such as adenomas, apoplexy, or hypophysitis. Also, since survival is usually short and clinical conditions of the patient may be poor, transsphenoidal surgery may not be mandatory. Of the 31 reported cases, only one-third (29%, n = 9) reported histopathological confirmation of pituitary lymphoma infiltration [6, 7, 12, 16, 19, 20, 24, 26, 27]. The same proportion was seen in our case series, and only in case 3 was pituitary biopsy considered necessary.

Usually, the prognosis is poor when the pituitary is already affected by lymphoma infiltration [37]. However, full endocrine recovery was found in 12% (n = 4) after treatment, and tumor regression on MRI scan was observed in 22% of patients (n = 7). In our series, after 4 months of chemotherapy, case 3 had no further lesions on MRI scan. Mortality was reported in 44% of the 34 patients (n = 15). The mortality in our series was 100% at follow-up, contrary to the previously reported cases. Our institution is a referral center for people with low socioeconomic status; hence they usually delay seeking medical attention, therefore diseases are diagnosed at later stages. These barriers in access to health care could explain the higher mortality in our population.

## Conclusion

We presented 2 cases of large B-cell NHL and 1 of mixed cellularity classic HL with pituitary anterior and posterior infiltration. Also, information about 31 cases were summarized. DI, central hypothyroidism, and central AI were the most common syndromes reported related to lymphoma infiltration. Clinical presentation, imaging, but mainly therapeutic response is important to confirm diagnosis. Pituitary gland biopsy is rarely necessary since patients have poor survival and prognosis in the context of advanced-stage systemic disease.

## Disclosures

The authors have no conflicts of interest to declare.

## Data Availability

The data supporting the findings of this study are available from the corresponding author on request.

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