Primary pituitary diffuse large B-cell lymphoma with somatotroph hyperplasia and acromegaly: case report

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma and comprises approximately 30% of all lymphomas. Patients typically present with a nonpainful mass in the neck, groin, or abdomen associated with constitutional symptoms. In this report, however, the authors describe a rare case of a 61-year-old woman with hyperprolactinemia, hypothyroidism, and acromegaly (elevation of insulin-like growth factor-1 [IGF-1]) with elevated growth hormone–releasing hormone (GHRH) in whom an MRI demonstrated diffuse enlargement of the pituitary gland. Despite medical treatment, the patient had persistent elevation of IGF-1. She underwent a transsphenoidal biopsy, which yielded a diagnosis of DLBCL with an activated B-cell immunophenotype with somatotroph hyperplasia. After stereotactic radiation therapy in combination with chemotherapy, she is currently in remission from her lymphoma and has normalized IGF-1 levels without medical therapy, 8 months after her histopathological diagnosis. This is the only reported case of its kind and displays the importance of a broad differential diagnosis, multidisciplinary evaluation, and critical intraoperative decision-making when treating atypical sellar lesions.

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KEY WORDS pituitary surgery; lymphoma; B-cell; somatotroph hyperplasia

DIFFUSE large B-cell lymphoma (DLBCL) is the most common form of lymphoid malignancy and most frequent type of non-Hodgkin lymphoma (NHL) in the world across age and demographics;^{15,43} it accounts for approximately 30% of all lymphomas. DLBCL is most commonly found in middle-aged or elderly individuals, with a median age at diagnosis in the sixth decade of life. Men are at slightly higher risk than women.¹⁸ Patients commonly present with a painless mass in the neck, groin, or abdomen associated with an array of constitutional symptoms, including fever, weight loss, night sweats, and fatigue. Central nervous system involvement may be observed in 2%–5% of cases; however, DLBCL presenting as a primary CNS lesion is quite rare, representing less than 1% of all primary brain tumors.¹⁴ Primary CNS presentation is usually associated with immunosuppression but has recently been identified with increasing frequency in immunocompetent individuals.¹⁴

Although the WHO classifies DLBCL as a single disease entity, there is significant variation in clinical presentation, behavior, response to treatment, and long-term out-

comes.³⁶ DLBCL is typically treated with a combination of anthracycline chemotherapy and immunomodulatory medications,^{7,13,29,30,37} with nearly 60%–70% of patients achieving a cure.³⁶

In this paper we describe a unique case of a 61-year-old woman diagnosed with a pituitary DLBCL, an activated B-cell immunophenotype, and growth hormone hyperplasia. Because this is the only reported case of its kind, we review the entity in the context of the pertinent literature and describe its management.

Case Report

History and Presentation

A 61-year-old, previously healthy woman presented with worsening headaches. She had laboratory evidence of elevated prolactin of 63 ng/ml (reference 2.8–26.0 ng/ml) and hypothyroidism (thyroid-stimulating hormone [TSH] 0.03 mU/L [reference 0.35–4.94 mU/L] and free thyroxine 0.45 ng/dl [reference 0.71–1.85 ng/dl]). Additionally, she had an elevation in insulin-like growth factor-1 (IGF-

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; DLBCL = diffuse large B-cell lymphoma; GHRH = growth hormone–releasing hormone; IGF-1 = insulin-like growth factor-1; NHL = non-Hodgkin lymphoma; PCNSL = primary central nervous system lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; SIADH = syndrome of inappropriate antidiuretic hormone; TSH = thyroid-stimulating hormone.

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FIG. 1. Coronal preoperative T2-weighted (A), postcontrast (B), and sagittal T2-weighted FLAIR (C) MRI of the patient's brain demonstrating a T2-isointense, homogeneously enhancing $12.8 \times 11.7 \times 11.8$ -mm sellar mass with no evidence of pituitary stalk displacement. Overall features were suggestive of pituitary hyperplasia/adenoma.

1) to 342 ng/ml (reference 75–263 ng/ml), with a growth hormone level of 4.85 ng/ml (reference 0.05–8.00 ng/ml). Magnetic resonance imaging of the brain demonstrated a diffusely enlarged pituitary gland (Fig. 1) concerning for hyperplasia. Because she did not have a clearly defined pituitary lesion but rather the appearance of hyperplasia, we measured the level of growth hormone–releasing hormone (GHRH) and found it was elevated at 56 pg/ml. After the initial evaluation, the patient was started on somatostatin injections in an effort to lower her IGF-1 level. She was also started on a regimen of cabergoline but reported an allergic reaction and the treatment was stopped. Levothyroxine was initiated to treat her central hypothyroidism.

Three months later, the patient's prolactin and thyroid hormone levels were within normal limits but she had persistent enlargement of the pituitary gland (Fig. 2) and her IGF-1 level had elevated further to 424 ng/ml. Given these findings, she was advised to undergo transsphenoidal biopsy of the pituitary gland for diagnostic purposes.

Surgical Intervention

The patient underwent a transsphenoidal biopsy of the pituitary gland using a microsurgical technique and stealth guidance. Notably, there was a small dehiscence in the floor of the sella that was used as an opening. The pituitary gland had an irregular, coarse appearance. It appeared mottled, and several biopsies were taken and sent for permanent pathology. Based on the preoperative imag-

ing, the gross appearance of the gland, and the absence of obvious adenoma, we judged that this was a diffuse process; thus, we harvested an abdominal fat graft and proceeded with closure.

Pathological Analysis

The final pathology report identified DLBCL with activated B-cell immunophenotype (CD10-negative, focal Bcl-6-positive, MUM-1-positive; Fig. 3). Additionally, the lymphoma expressed Bcl-2 with an estimated proliferative index of 90% by MIB-1 immunostaining. C-myc staining highlighted 20% of the neoplastic cells. On microscopic examination, there was evidence of pituitary gland with associated fragments of fibrous tissue and a diffuse infiltrate of large, atypical lymphoid cells (Fig. 3A). The lymphoid cells were pleomorphic with irregular nuclear contours, vesicular chromatin, prominent nucleoli, and scant to moderate amounts of cytoplasm (Fig. 3B–D). Immunohistochemical staining demonstrated diffuse positivity for CD45 and CD20 without expression of CD30, anaplastic lymphoma kinase, S100, cytokeratin, CD2, or CD3. The large atypical cells were negative for CD10, with focal expression of Bcl-6 and diffuse expression of MUM-1 (not shown). Additionally, they expressed Bcl-2, and approximately 20% exhibited positivity for C-myc. Because of the patient's endocrinopathies, immunohistochemical staining was also performed for reticulatin, adrenocorticotrophic hormone (ACTH), growth hormone,

FIG. 2. Coronal 3-month interval preoperative T2-weighted (A), and coronal (B) and sagittal (C) postcontrast MRI of the brain demonstrating subtle enlargement of the sellar mass with current dimensions of $14.5 \times 11.6 \times 11.7$ mm. Overall features were suggestive of a neoplastic origin of the lesion.

FIG. 3. Photomicrographs from the pathological analysis. **A:** Low-power view of the pituitary gland demonstrating a highly cellular, infiltrative process of neoplastic cells obliterating the normal pituitary architecture. There is minimal residual pituitary gland tissue present in this field of the tissue. Bar = 100 μ m. **B:** High-power view of panel A demonstrating highly atypical cells with marked nuclear atypia, irregular nuclear contours, and prominent nucleoli. These represent the infiltrating DLBCL that stained in the pituitary. In the center of the photo and toward the top left of the field are 3 residual pituitary gland cells that show abundant eosinophilic cytoplasm with cytoplasmic vacuolations. Bar = 20 μ m. **C:** Medium-power view of the pituitary gland adjacent to the focus heavily involved by lymphoma, demonstrating that the vast majority of residual pituitary gland is composed of pituitary acidophils. Minimal pituitary basophils are present in this field, a finding consistent with other areas of the tissue submitted for evaluation. The DLBCL cells are infiltrating the residual pituitary tissue. Bar = 50 μ m. **D:** High-power view of panel C showing a predominance of pituitary acidophils and 1 small cluster of basophils. The architecture is being disrupted by the infiltrating neoplastic DLBCL, associated lymphoplasmacytic infiltrate, and fibrosis. Bar = 20 μ m. **E:** Low-power view of the pituitary demonstrating diffuse positive staining for human growth hormone on immunohistochemical stain in the residual pituitary gland. The light purple cells in the background are the neoplastic B-cells infiltrating between the pituitary acinar structures. This finding was observed throughout the tissue submitted for examination. Bar = 100 μ m. **F:** High-power view of panel E demonstrating the granular cytoplasmic immunohistochemical staining pattern for human growth hormone in the residual pituitary gland. The light purple cells in the background are the neoplastic B-cells and pituitary parenchyma. Bar = 20 μ m. Figure is available in color online only.

and prolactin. The residual pituitary gland showed retention of the reticulin network, consistent with pituitary hyperplasia. There were more pituitary gland cells staining positive for growth hormone and scattered positivity for ACTH and prolactin staining (Fig. 3E and F). Overall, this pathological analysis was consistent with somatotroph hyperplasia, rather than a clonal production of growth hormone-secreting cells.

The pituitary gland is normally composed of acidophils (somatotrophs and lactotrophs) and basophils (thyrotrophs, corticotrophs, and gonadotrophs). The nomenclature reflects how these two types of cells retain the H & E stain. The acidophilic cells release growth hormone and prolactin. The basophilic cells release ACTH, luteinizing hormone, follicle-stimulating hormone, and TSH. The histology in this case demonstrates an acidophil predominance and minimal basophils (Fig. 3), correlating with the elevated growth hormone and hyperprolactinemia in conjunction with hypothyroidism, indicating concordance between the histological, serological, and physical examination findings.

Hospital Course and Follow-Up

Postoperatively, the patient had an uneventful hospital course and was discharged on postoperative Day 3. There was no evidence of diabetes insipidus, syndrome of inappropriate antidiuretic hormone (SIADH) release, or additional endocrinopathy. Her postoperative growth hormone level was 2.44 ng/ml, and her prolactin level remained normal. She was maintained on levothyroxine therapy, as she continued to have a low TSH level.

Shortly after final pathological diagnosis was obtained, the patient underwent PET/CT imaging of her whole body, which demonstrated hypermetabolism in the pituitary gland as well as a prominent cervix and a 2.3-cm hypermetabolic area in the posterior uterine fundus. Bone marrow biopsy and lumbar puncture revealed normal findings, ruling out disseminated disease. Human immunodeficiency virus and hepatitis B testing performed after biopsy were negative.

A gynecological consultation indicated the lesion was likely a benign uterine fibroid and nabothian cyst and not metastatic disease to the cervix; the patient's lymphoma was graded as Stage 1E, and the goal of adjuvant therapy was curative. She subsequently underwent 3 cycles of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) followed by 3600 cGy of stereotactic radiation with 180 cGy for 20 fractions over 27 days. In planning for radiation therapy, the enhancing area on MRI was used as a target with an additional 5-mm margin, resulting in a planning treatment volume of 9.748 cm³.

The patient underwent MRI of the brain before beginning stereotactic radiosurgery, which demonstrated no evidence of residual or new enhancement. Thus, she likely had a response to R-CHOP prior to radiation therapy. Radiation was used in this setting to achieve a cure in this case despite her Stage 1E DLBCL because of the atypical location with lack of systemic involvement and no additional CNS disease.

MRI of the brain approximately 6 months after her initial pathological diagnosis and 2 months after completing radiation therapy demonstrated no evidence of mass lesion or enhancement in the pituitary gland (Fig. 4). Her IGF-1 level normalized within 5 months of beginning radiation and chemotherapy without any somatostatin analog therapy, and she developed no further clinical features of acromegaly. Additionally, her prolactin level has remained normal. She continues to take thyroid hormone replace-

FIG. 4. Postoperative coronal T2-weighted (A), and coronal (B) and sagittal (C) postcontrast MRI of the brain demonstrating complete resolution of the sellar mass with no evidence of residual disease.

ment with no additional endocrinopathies or significant hormonal deficits after successful completion of her radiation therapy and chemotherapy.

Discussion

We present a rare case of DLBCL with somatotroph hyperplasia, which was apparently caused by an increased circulating level of GHRH. This is the first reported case of this pathology and presents an interesting diagnostic challenge. DLBCL is the most common type of NHL; it typically is responsive to chemotherapy and is considered curable.²⁵

Primary central nervous system lymphoma (PCNSL) can present as a primary pituitary lesion^{2,10,11,17,19,20,22,32–34,39,41,42} (and Spina et al., presentation at the International Symposium on Neuroendocrine-Oncology: Biological and Clinical Aspects, Turin, 2000) or as a secondary area of localization by infiltration of the sella turcica.^{1,4,6,16,23,28,31,38,40} In an autopsy series of 265 patients, 38 cases of PCNSL were discovered, but there was no evidence or mention of pituitary dysfunction during the individuals' lifespans.²⁶ Within the literature surrounding PCNSL of the pituitary gland, several risk factors have been reported to contribute to its formation, including acquired immunodeficiency syndrome, pituitary adenomas, and lymphocytic hypophysitis.²⁴ In this case, there was no history of immunodeficiency or lymphocytic hypophysitis, which occurs predominantly in females but is associated with pregnancy and the postpartum period.

Pituitary tumors have a prevalence of up to 20% of the population.⁹ As the most common sellar mass, pituitary adenomas account for up to 10%–15% of all intracranial neoplasms;¹² however, atypical intrasellar masses can also occur. The differential diagnosis for such lesions include germ cell tumor, glioma, meningioma, metastatic tumor, vascular lesion, and granulomatous, infectious, and reactive inflammatory processes.¹⁰

Although lymphomas of the pituitary have been described previously, this is a rare case of PCNSL. In general, PCNSL may not be as rare as first described and is now believed to represent 3% of all intracranial neoplasms.⁸ A postmortem topographic study of PCNSL and its distribution in the brain revealed pituitary gland involvement in 5 (25%) of 22 cases, typically involving the posterior lobe, but sparing the anterior lobe.²⁸ Pituitary DLBCL as a subset

of PCNSL has also been described previously,^{2,10,11,19,22,34,39} but not in the context of somatotroph hyperplasia and persistently elevated IGF-1, caused by elevation in GHRH.

GHRH has been shown to be elevated in some cases in a variety of malignancies including NHL as well as breast, colorectal, renal, and neuroendocrine tumors.^{27,35} Evidence supports the mechanism that GHRH is produced by tumor cells and acts in an autocrine fashion to promote tumor growth. In fact, GHRH receptor antagonists have demonstrated efficacy as therapeutic inhibitors of tumor growth.^{27,35} In the case of our patient, ectopic malignancy producing GHRH was effectively ruled out through thorough whole-body imaging, including PET CT. Therefore, it is reasonable to postulate that the patient's increased GHRH was produced by the lymphoma cells and that the high level acted directly upon nearby somatotrophs to cause hyperplasia and increased growth hormone production, leading to increased IGF-1 level and clinical acromegaly. Systemic lymphoma resulting in elevated serum growth hormone levels³ as well as GHRH production by malignancies has been previously reported (as stated above); however, elevated circulating IGF-1 levels and clinical acromegaly in the setting of primary pituitary DLBCL have not previously been reported. There have been several other cases of primary intrasellar DLBCL reported, but none has shown evidence of clinical acromegaly and somatotroph hyperplasia (Table 1). We suggest that the proximity of the lymphoma cells to the somatotrophs may have been crucial to the development of this phenomenon. A 71-year-old woman who presented with acromegaly was found to have evidence of 3 discrete pathological processes: primary pituitary lymphoma, lymphocytic hypophysitis, and an intrasellar adenoma.²¹ The current case contrasts with this case, however, because of the lack of a discrete adenoma to explain the elevation in IGF-1.

It is also interesting to note that the IGF-1 level was refractory to somatostatin analog therapy. This was perhaps due to the lymphoma cells secreting a constant (rather than pulsatile) level of GHRH. GHRH prohibits somatostatin action, and the two are secreted in alternating pulsatile fashion under normal physiological conditions.

In addition, the association of pituitary adenomas with lymphoma also may provide additional insight into this rare case. Lymphoma cells possess endocrine hormone receptors, and growth of both T and B lymphoma cells can be stimulated by prolactin and growth hormone.⁵ In addition, the expression of mutated adhesion molecule

TABLE 1. Reported cases of primary B-cell lymphoma of the pituitary

Authors & Year	Age (yrs), Sex	Imaging Findings	Confirmed Pathology/Histopathology	Concomitant Endocrine Dysfunction
Freda & Post, 1999	48, M	Mass involving the sella, sphenoid sinus (MRI)	Large cell, B-cell type	None
Landman et al., 2001	86, F	Sellar mass w/ an enlarged pituitary fossa (MRI)	NHL-large cell, B-cell type	Central hypothyroidism, SIADH
Gottfredsson et al., 1996	48, M	Enhancing mass in the pituitary (CT)	DLBCL	None
Shaw et al., 1997	73, F	Mass in the sphenoid sinus, thickening of the pituitary stalk (MRI)	Low-grade NHL w/ mostly B-cell markers	Panhypopituitarism, diabetes insipidus, increased prolactin
Au et al., 2000	82, M	Mass enlarging the pituitary fossa (MRI)	DLBCL w/ pituitary adenoma	Panhypopituitarism, pathology w/ weak TSH positivity
Mathiasen et al., 2000	65, M	Diffuse enlargement of the pituitary gland (MRI)	DLBCL	Panhypopituitarism
Current case	61, F	Diffuse enlargement of the pituitary gland (MRI)	DLBCL	Acromegaly; somatotroph hyperplasia

on adenomatous pituitary cells may act as a lymphocyte “homing” signal, and growth hormone and prolactin may have mitogenic effects on lymphoma cells and normal human lymphocytes.^{5,24}

It is essential to consider atypical masses of the sellar region in the assessment of patients with hormone dysfunction and lack of response to first-line medical therapy. In addition, surgical biopsy can provide invaluable information in making a challenging diagnosis. In this paper we describe a unique case of a 61-year-old woman diagnosed with DLBCL, an activated B-cell immunophenotype, and somatotroph hyperplasia caused by elevated GHRH and resulting in elevated circulating IGF-1 and clinical acromegaly. This is the only reported case of its kind and displays the importance of a broad differential diagnosis, multidisciplinary evaluation, and critical intraoperative decision-making when treating atypical sellar lesions.

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Author Contributions

Conception and design: Couldwell, Ravindra, Raheja. Acquisition of data: Ravindra, Raheja. Analysis and interpretation of data: all authors. Drafting the article: Ravindra. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Couldwell. Study supervision: Couldwell.

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