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CLINICAL CASE REPORT

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Pineal Diffuse Large B-Cell Lymphoma Concomitant With Pituitary Prolactinoma: Possible Correlation Between 2 Distinguished Pathologies

A Case Report

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Abstract: This is the first reported case of pineal lymphoma with concomitant prolactin-producing pituitary adenoma.

A 51-year-old male experienced worsening headaches accompanied by nausea, diplopia, and memory loss for 1 month. Cranial nerve examination revealed bilateral upward gaze limitation with convergence impairment, which is known as Parinaud syndrome. Magnetic resonance images revealed a mass in the pineal gland with a coexisting mass within the enlarged sella fossa. Hormone analysis revealed hyperprolactinemia. The pineal mass was removed without injuring the hypothalamus, brain stem, or any neighboring vessels. Pathology examination confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL) involving the pineal gland. After further studies, the pineal lymphoma was determined to be a secondary tumor from a gastric primary tumor. The patient died 6 months after diagnosis due to systemic progression of DLBCL.

Although the mechanistic link between hyperprolactinemia and lymphoma progression has not been clarified on a clinical basis, high prolactin levels may contribute to the rapid progression and therapeutic resistance of the lymphoma.

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Abbreviations: CNS = central nervous system, DLBCL = diffuse large B-cell lymphoma, IHC = immunohistochemistry, MR = magnetic resonance, PRL = prolactin, PRL-R = prolactin receptor.

INTRODUCTION

Cerebral lymphoma is a malignant lymphocytic neoplasm that can occur as a primary tumor or as a secondary manifestation of systemic disease. Once considered a rare neoplasm, the incidence of central nervous system (CNS) lymphoma has increased significantly in recent decades.[1] At initial diagnosis, a primary CNS lesion appears in approximately 1% to 2% of patients with non-Hodgkin lymphoma.[2] Systemic lymphoma spreads to the CNS in 5.5% to 9.4% of cases and is associated with a poor prognosis.[3,4] The occurrence of malignant lymphoma in the pineal region is extremely rare. Only 10 cases of primary or secondary pineal lymphomas, including the case in this study, have been reported in the literature to date.[5–13]

Neuroendocrine and immune responses mutually affect each other via various interactions between the hormones/respective receptors and the immune system.[14] Furthermore, elevated prolactin (PRL) levels are associated with the progression of hematologic diseases including multiple myeloma, acute myeloid leukemia, and non-Hodgkin lymphoma.[15–17] Here, we report a case of pineal lymphoma as the first manifestation of gastric lymphoma and discuss the possible role of concomitant pituitary prolactinoma on lymphoma.

CASE PRESENTATION

A 51-year-old male experienced worsening headaches for 1 month, which were accompanied by nausea, diplopia, and mild memory loss. He had no significant medical history and was not taking any medications including antipsychotics. On admission, the liver and spleen were not palpable, and there were no palpable superficial lymph nodes. Neurological examination revealed no evidence of impaired mental status, gait difficulties, or sensory or motor deficits. Positive neurological findings included bilateral upward gaze limitation with convergence impairment, also called Parinaud syndrome. Magnetic resonance (MR) image of the brain revealed a $2 \times 2 \times 2$ cm mass in the pineal gland with a concomitant $1.5 \times 1.5 \times 1.2$ cm mass within the enlarged pituitary fossa (Figure 1A–D). The pineal mass showed iso- to hypointensity on T_1- and T_2-weighted MR images and heterogeneous enhancement by gadolinium administration. It was a multilobulated mass that extended into the hypothalamus and midbrain. The lesion showed perilesional edema and internal calcification. Obstructive hydrocephalus due to stenosis of the aqueduct of Sylvius was also seen. Laboratory findings upon admission included a $6.7 \times 10^3/mm^3$ white blood cell count with a normal differentiation, a hemoglobin level of 10.8 g/dL, and a platelet count of
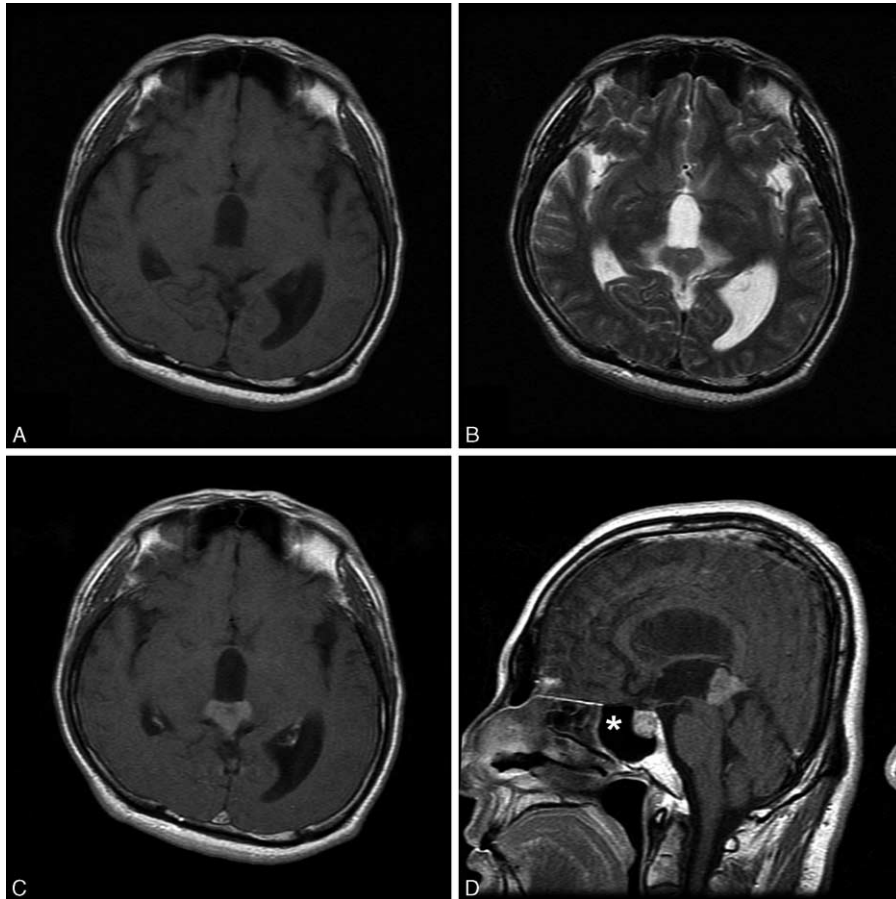
FIGURE 1. Preoperative magnetic resonance (MR) imaging. (A) A hypo- to isointense mass was detected at the pineal region on the T_1-weighted image. (B) Marked peritumoral edema was shown surrounding the pineal mass on the T_2-weighted image. (C) Axial image with gadolinium enhancement demonstrated multilobulation and heterogenous enhancement of the pineal mass, with a margin indistinct from the surrounding hypothalamus and midbrain, and hydrocephalus caused by obstruction of the aqueduct of Sylvius. (D) Note a strongly enhanced mass located entirely within the enlarged sellar turcica (asterisk).

$360 \times 10^3/mm^3$. Hormonal analysis indicated hyperprolactinemia (977.7 ng/mL; normal, 2.8–29.3 ng/mL). The patient's serum thyroid-stimulating hormone (TSH) and free T4 values were 0.652 μIU/mL (normal, 0.8–1.71 μIU/mL) and 0.770 ng/dL (normal, 0.4–4.8 ng/dL). Coagulation, hepatic, and renal profiles were within normal limits. A serologic study for human immunodeficiency virus was negative. Tumor markers for a pineal mass, such as α-fetoprotein, human chorionic gonadotropin, and carcinoembryonic antigen, were within normal ranges. Due to the presumptive diagnosis of a nongerminomatous, parenchymal, or glial tumor on the pineal gland, surgery was performed using the occipital transtentorial approach. A slightly hard, dark red mass was located in the pineal gland and posterior third ventricle. The mass had internal calcification and was easily demarcated from the peritumoral brain parenchyma. Some portions of the mass that adhered to surrounding venous structures required sharp dissection. Frozen biopsy diagnosis of the pineal lesion suggested a pineoblastoma. The mass was removed completely without injuring the hypothalamus, brain stem, or any neighboring vessels.

Histopathology revealed diffuse infiltration of large lymphocytes with vesicular nuclei, prominent nucleoli, and abundant cytoplasm. In some portions, the cells were arranged in sheets with a prominent starry-sky pattern and geographic coagulative necrosis. Interestingly, the well-known characteristics of perivascular infiltration of tumor cells were not identified, since the pineal parenchyma was almost completely replaced by neoplastic lymphocytes. An initial immunohistochemistry (IHC) panel was performed to exclude the diagnostic possibility of pineoblastoma and other germ cell tumors that frequently develop in the pineal gland. The tumor cells were all negative for synaptophysin, glial fibrillary acidic protein, pancytokeratin, and placental alkaline phosphatase. Instead, tumor cells showed strong positivity for B-cell markers including CD79a and CD20 but were negative for T-cell markers including CD3 and CD45RO. BCL2 was also positive, and the Ki-67 labeling proliferation index exceeded 50%. Pathology confirmed a diffuse large B cell lymphoma (DLBCL) involving the pineal gland. Additional IHC panel for DLBCL subdivision revealed BCL6 positivity, and CD10 and MUM1 nonreactivity (Figure 2A–D). Consequently, the immunohistochemical subgroup of the lymphoma was a germinal center-like DLBCL.[18]

Two weeks after the operation, the patient complained of gastric fullness and aggravated vomiting. Abdominal computed tomography revealed concentric wall thickening in the lower portion of the lesser curvature of the gastric body, but there was
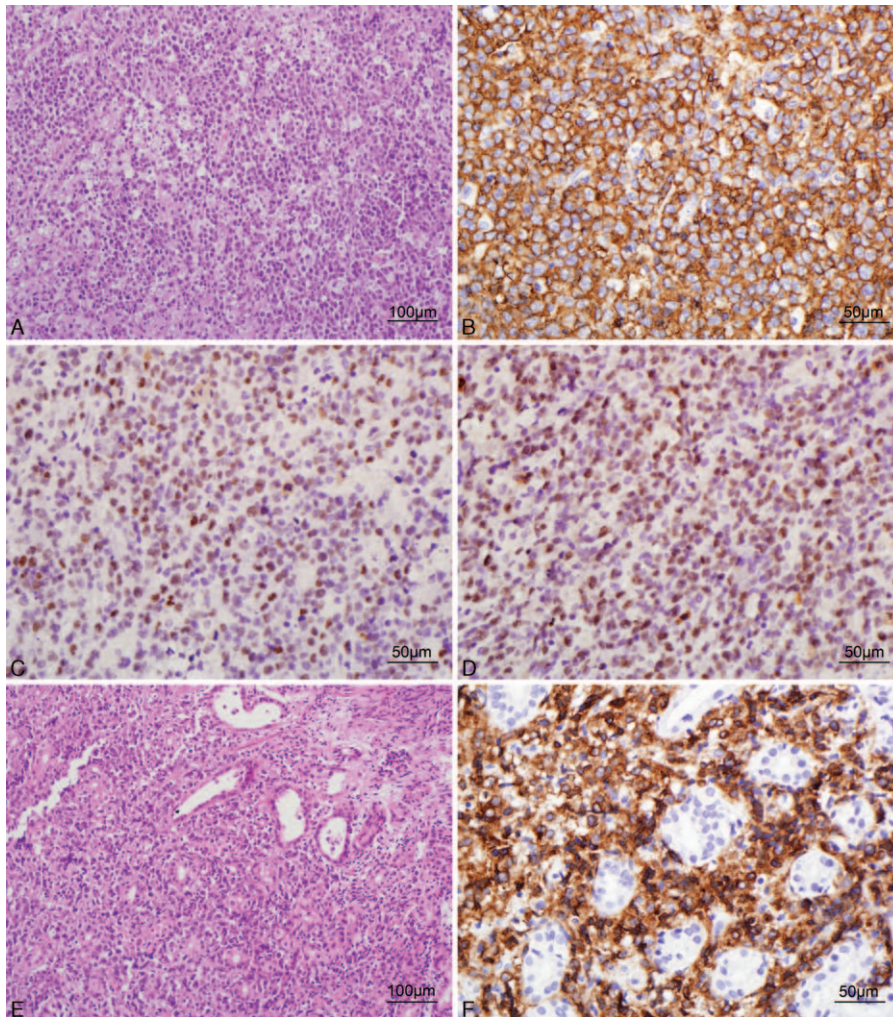
FIGURE 2. Microscopic characteristics of the pineal and gastric diffuse large B-cell lymphoma (DLBCL). (A) The pineal mass was composed of enlarged lymphocytes and scattered pale histiocytes featuring a starry-sky appearance (hematoxylin and eosin [H&E] staining, original magnification ×200). (B) The tumor cells were diffusely positive for CD20 (immunohistochemistry, ×400). (C) Approximately 40% of the tumor cells showed positivity for BCL6 (immunohistochemistry, ×400). (D) The Ki-67 proliferation index of the tumor exceeded 50% (immunohistochemistry, ×400). (E) The lymphoma cells were densely infiltrated between the remaining gastric glands (H&E stain, ×200). (F) The gastric lymphoma cells showed strong staining for CD79a (immunohistochemistry, ×400).

no evidence of enlarged lymph nodes or hepatosplenomegaly. Upper esophagogastroduodenoscopy showed a diffuse ulceroinfiltrative mass in the lesser curvature of the gastric body (Figure 3). Pathological diagnosis was DLBCL, identical to that of the previously removed pineal mass (Figure 2E and F). Other systemic evaluations, including chest and neck computed tomography scans and bone marrow biopsy, were normal. The PRL level gradually dropped to 459 ng/mL 3 months after the brain operation. After removal of the pineal gland mass, the patient was treated with 2 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by 1 cycle of high-dose methotrexate (3.5 g/m^2) chemotherapy. The patient was originally planned to be treated with 2 cycles of R-CHOP, followed by 4th infusion of high-dose MTX-based chemotherapy and additional 4 cycles of R-CHOP chemotherapy. However, further chemotherapy had to be discontinued after 1 cycle of high-dose MTX chemotherapy since the patient had neutropenia and general weakness. Two months after the

brain operation, the patient underwent an emergent operation for mechanical ileus due to a newly developed mass. Subsequently, the patient had aspiration pneumonia and showed progression of the brain lesion aggravated by CSF seeding. The patient died 6 months after initial diagnosis.

To evaluate the contribution of elevated PRL levels on the rapid progression of DLBCL, PRL expression in lymphoma cells was investigated by IHC. Both the pineal and gastric lesions were repeatedly negative for PRL staining (Figure 4A). For further evaluation of PRL receptor (PRL-R) expression, IHC and Western blot (WB) analysis were performed (dilution 1:200 for IHC, 1:2000 for WB; clone B6.2, catalogue no. MA5-11955, Thermo Fisher Scientific, Rockford, IL). WB was performed as described previously.[19] To validate the results, WB analysis using a representative lymphoma cell line, EG7 (kindly provided by Dr Yang Deok-Hwan, Chonnam National University), and IHC staining for PRL-R were performed in an additional 10 DLBCL cases (Table 1). As shown
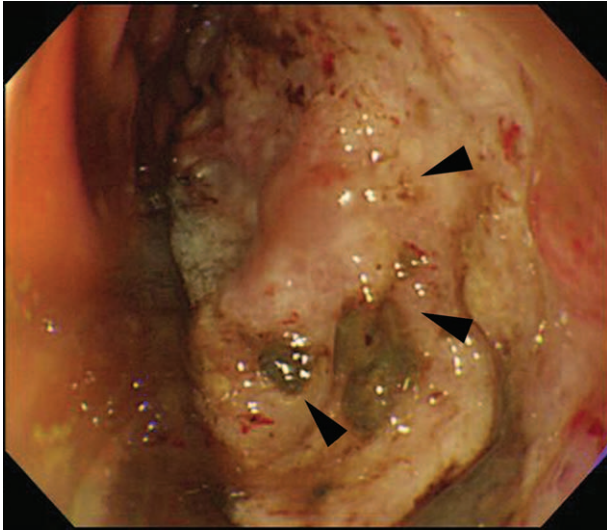
FIGURE 3. Esophagogastroduodenoscopy (EGD) showed a diffuse infiltrative mass with central ulceration (indicated by arrowheads) located in the lesser curvature of the gastric body.

in Figure 4A, surgical samples from primary gastric and metastatic pineal lesions stained positive for PRL-R. PRL-R expression in lymphoma cells was also shown in the EG7 lymphoma cell line by WB (Figure 4B). In addition, 9 of 10 cases displayed diffuse or patchy strong PRL-R positivity (Figure 5), and the remaining case showed localized immunoreactivity around the vessels. The patients provided signed, informed consent, and the study was approved by the Institutional Review Board of the Chonnam National University Hwasun Hospital.

DISCUSSION

Primary CNS lymphomas (PCNSL) are supratentorial in approximately 60% of patients.[20] Despite the more common location of PCNSL in the supratentorial region, involvement of the pineal gland is extremely rare. In a meta-analysis of PCNSL, only 0.5% of enrolled cases (2 of 424 cases) had tumors in the pineal location.[21] Secondary CNS involvement is infrequent in DLBCL, with an incidence range of 5% to 25% reported in studies assessing different risk factors and diagnostic tools.[22–24]
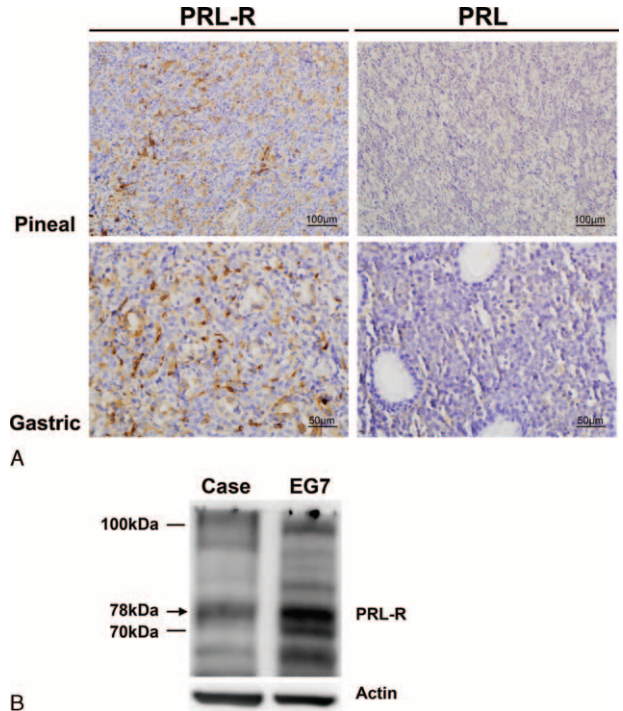
FIGURE 4. Expression of prolactin receptor (PRL-R) in the current case. (A) Immunohistochemistry of PRL-R revealed a strong positivity in both primary gastric and metastatic pineal lymphomas (immunohistochemistry, ×200 and ×400, respectively). There was no expression of prolactin in the same samples (immunohistochemistry, ×200 and ×400, respectively). (B) Western blot analysis revealed PRL-R expression in the pineal lymphoma. This positive reaction was also noted in the lymphoma cell line EG7.

The pineal region is one of the rarest locations for intracranial metastasis of systemic malignancies, with an incidence range of 1.8% to 4% of all intracranial metastases.[25–28] Approximately half of the cases have no other metastases within the brain, as in this case.[25] Hematogenous spread through the posterior choroidal artery is suggested as the pathomechanism for pineal metastasis, given that the pineal gland is a circumventricular organ of the brain lacking a blood–brain barrier.[28,29]

TABLE 1. Brief Summary of Additional 10 Cases of DLBCL

Sample Mark	Age	Sex	Location	IHC Result for Prolactin Receptor
A	72	M	Neck lymph node	+, Diffuse strong
B	57	M	Tongue	+, Diffuse strong
C	73	F	Neck lymph node	+, Patchy strong
D	71	M	Neck lymph node	+, Patchy strong
E	75	M	Neck lymph node	+, Patchy strong
F	73	F	Inguinal lymph node	+, Patchy strong
G	63	F	Neck lymph node	+, Patchy strong
H	73	F	Neck lymph node	+, Patchy strong
I	63	F	Inguinal lymph node	+, Patchy strong
J	73	M	Neck lymph node	+, Localized around vessels

DLBCL = diffuse large B-cell lymphoma, ICH = immunohistochemistry.
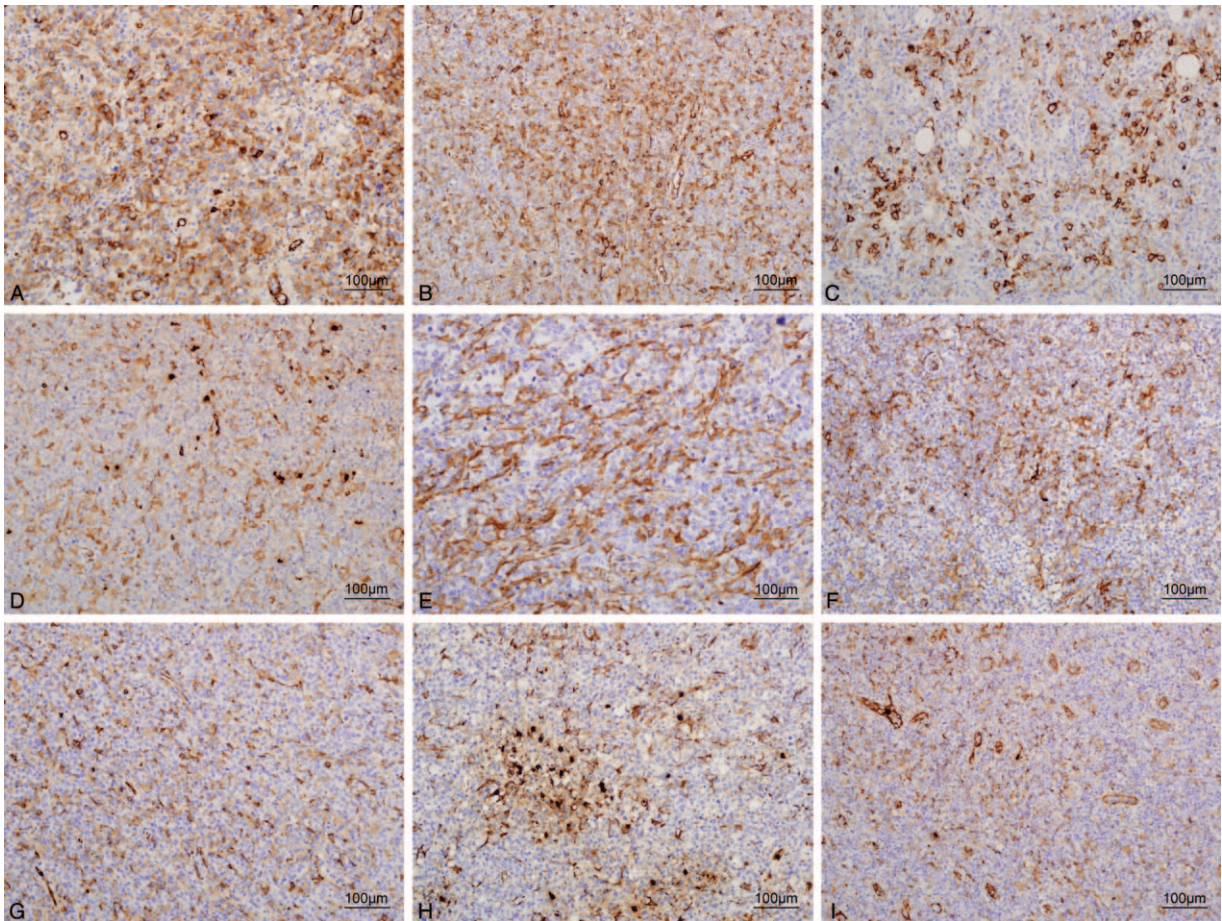
FIGURE 5. Immunohistochemistry of the prolactin receptor (PRL-R) in additional diffuse large B-cell lymphoma samples. Nine out of 10 selected cases showed positive immunoreactivity with variable portions of tumor components.

Even though it is an isolated event, CNS involvement represents widespread disease progression and has the worst clinical outcome, with less than 10% of patients surviving 1 year.[4,30,31] Of the 10 reported cases of pineal lymphoma, 6 involved multiple locations, and 2 were secondary, with 1 retroperitoneal primary and 1 gastric primary (Table 2). The majority of the cases (6 out of 8 with determined histological types) were of a B-cell lineage, and the overall clinical progression seemed to be fatal, but follow-up information was insufficient.

In CNS lymphoma, concurrent brain tumor types including astrocytoma,[32] meningioma,[33] and pituitary adenoma[34−36] have been reported. Interruption of the inhibitory pathway between the hypothalamus and pituitary gland was proposed as the putative pathogenesis for the development of pituitary adenoma in hypothalamic PCNSL.[34] In contrast, lymphoma development may be stimulated by microenvironmental alterations or hormones produced by the pituitary adenoma.[35] Another reported case of intermingled adenoma with lymphoma suggested a strong connection between pituitary adenoma and lymphoma in the same location.[36]

Whereas PRL-R is expressed in immune cells universally, the expression of human PRL is found mainly in T lymphocytes.[37] In addition, PRL production is evident in normal extrapituitary sites, including the decidua, myometrium, breast, prostate, brain, and malignant cells.[38,39] Although the precise function of PRL in immune cells is not clear, PRL has an important role in immunomodulation and lymphoid cell proliferation, in addition to the promotion of normal hematopoiesis.[40−42] PRL promotes both cell-mediated and humoral immune responses through signaling pathways, including JAK/STAT and mitogen-activated protein kinase, resulting in target gene expression,[43] stimulation of B- and T-cell proliferation, proinflammatory cytokine production, and B-cell growth arrest.[14] PRL can act as a survival (antiapoptotic) factor or as a mitogen, as exemplified in the lactating mammary gland, Nb2 lymphoma cells, and breast cancer cells.[38]

The presence of elevated serum PRL levels in the context of hematological malignancy is still controversial. A small number of previous studies reported elevated PRL levels in lymphoma patients,[16,44] as well as in acute myeloid leukemia patients.[17,45] Pathological hyperprolactinemia was shown to be associated with a reduction in natural killer cell number and function.[46] In addition to a direct mitogenic effect, PRL also has the capacity to inhibit cell death induced by cisplatin, doxorubicin, taxol, and other agents in cancer cells as exemplified by breast cancer research,[47,48] through drug detoxification arising from PRL-induced activation of glutathione S-transferase,[48] or potentially via PRL-mediated upregulation of antiapoptotic proteins such as BCL2.[49]

TABLE 2. Clinoco-Radiological Characteristics of Reported Cases of Pineal Lymphoma

Author/Year	Age/Sex	Symptoms	Imaging Findings	Origin	Histological Type	Clinical Outcome
Matsuno et al, 1993[8]	21/M	Headache, nausea, polyuria, reduced body hair, and libido	Multiple lesions; involving suprasellar region and medullar oblongata (MR)	Primary	T cell	Alive; no recurrence for 10 months
Popovic et al, 1993[9]	NA	NA	NA	Primary	Non-Hodgkin	NA
Amagasa et al, 1996[7]	15/M	Headache, urinary incontinence, gait disturbance, Parinaud sign	Diffuse enhancement with calcification (CT)	Primary	Immunoblastic B cell	Alive; spinal metastasis after 11 months
Grimoldi et al, 1998[6]	52/M	Headache, obnubilation, apathy, Parinaud sign	Homogenous enhancement (CT)	Primary	NA	NA
Freedman et al, 2001[29]	71/F	Disorientation, memory loss, Parinaud sign	1.5 cm enhancing mass; retroperitoneal primary (MR)	Secondary	Diffuse large B cell	Dead after 4 months
Karikari et al, 2007[11]	4/M	Seizure, altered mental status	Heterogeneously enhancing mass with leptomeningeal nodular enhancement (MR)	Primary	ALK-1 + anaplastic large cell	Transferred to other hospital
Endo et al, 2009[10]	31/M	Headache, nausea, gaze limitation	Multiple enhanced lesions; involving cranial nerves (MR)	Primary	Diffuse large B cell	Transferred to other hospital
Yoshida et al, 2014[12]	62/M	Dysphagia, hoarseness	Cystic mass with enhancing nodule; involving cranial nerves (MR)	Primary	Diffuse large B cell	Transferred to other hospital
Vasudevan et al, 2015[13]	58/F	Head ache, diplopia, behavioral changes, gait disturbance	Homogenously enhancing mass (CT)	Primary	Diffuse large B cell	NA
Current case	51/M	Diplopia, nausea, memory impairment, Parinaud sign	Multilobulated heterogenously enhancing mass; gastric primary (MR)	Secondary	Diffuse large B cell	Dead after 4 months

CT = computed tomography, MR = magnetic resonance, NA = not available.

In this case, the endosellar mass was diagnosed as a prolactinoma based on an elevated PRL > 300 ng/mL and relevant MR imaging,[50,51] even without pathological confirmation. There were a couple of reasons for that the pituitary tumor was prolactinoma. First, IHC staining using PRL antibody was repeatedly negative in the pineal and gastric lesions. It seemed unlikely that PRL was massively secreted from the pituitary lesion if the pituitary gland also had a lymphoma. Second, serum PRL levels exceeding 300 ng/mL are almost always caused by a pure prolactinoma or a mixed pituitary adenoma with a lactotrophic component.[50,51] There are variable causes of hyperprolactinemia including drugs, pregnancy, nipple stimulation, and pituitary PRL secreting adenoma. Serum PRL levels in patients with prolactinoma can range from minimally elevated to 50,000 ng/mL, but the PRL levels rarely exceed 200 ng/mL in hyperprolactinemia due to other causes. Three months after complete removal of the pineal lymphoma, the PRL level gradually dropped to 459 ng/mL without specific treatment for the prolactinoma. This finding corroborated a previous report that hyperprolactinemia is associated with lymphoma.[16,44] The studies described above showed that certain subpopulations of lymphocytes synthesize and secrete biologically active PRL and that PRL can act as an autocrine and/or paracrine factor to modulate the activities of cells of the immune system. Despite repeated immunostaining in the current case, the tumor cells did not stain for PRL. In comparison, some lymphoma samples showed PRL-R expression. Presumably, shrinkage of the lymphoma volume may have affected the functional aspects of the prolactinoma. In addition, it is likely that the persistent hyperprolactinemia may have affected the chemoresistance of the DLBCL and have contributed to the fatal deterioration of the patient's condition.

In conclusion, this is the 1st clinical report of concurrent prolactinoma and pineal lymphoma to our knowledge. This report raises questions about the mutual interaction between lymphoma progression and hyperprolactinemia. The occurrence of lymphoma in the clinical context of hyperprolactinemia may have important implications. Any clinical condition that results in elevated PRL levels needs to be controlled. In small clinical studies on breast cancer, patients treated with antiprolactinemic agents in combination with docetaxel responded better than those treated with docetaxel alone.[52,53] Additional research and clinical data are required to clarify the exact correlation between DLBCL progression and hyperprolactinemia.

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