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Case Report

ICAM1-Negative Intravascular Large B-Cell Lymphoma of the Pituitary Gland: A Case Report and Literature Review

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ABSTRACT

Objective: Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive type of B-cell lymphoma with large cells growing within the lumen of blood vessels. Although previous reports revealed highly variable symptoms resulting from small-vessel occlusion by neoplastic cells in a variety of organs, there are few reports of IVLBCL with pituitary involvement.
Method: We present a case of IVLBCL with pituitary infiltration from our institution together with a literature review of similar cases to better understand this rare case of IVLBCL involving the pituitary gland.
Results: Our case and the pertinent literature demonstrated that IVLBCL with pituitary involvement predominantly occurred in women at a mean age of 64 years, and most of them showed panhypopituitarism that was reversible after standard therapy of rituximab-containing chemotherapy with intrathecal methotrexate. Notably, the pituitary biopsy in our case revealed that atypical large B-cells found within blood vessels and the pituitary gland were negative for intercellular adhesion molecule 1. Intercellular adhesion molecule 1-negative lymphoid cells may have contributed to panhypopituitarism by extravasation into the pituitary tissues, which do not have a blood-brain barrier and receive abundant blood flow.
Conclusion: IVLBCL of the pituitary gland is a rare lymphoma with nonspecific manifestations and a dismal prognosis. Recognition of the clinicopathological features is necessary for early clinical diagnosis and appropriate treatment.

Abbreviations: ACTH, adrenocorticotropic hormone; BAL, bronchoalveolar lavage fluid analysis; CRH, corticotropin-releasing hormone; FDG, ^{18}F-fluorodeoxyglucose; FSH, follicle-stimulating hormone; GH, growth hormone; GHRP2, growth hormone-releasing peptide 2; ICAM1, intercellular adhesion molecule 1; IVLBCL, intravascular large B-cell lymphoma; LDH, lactate dehydrogenase; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; MEAM, ranimustine, etoposide, cytarabine, and melphalan; MTX, methotrexate; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-hyper-CVAD/MA, rituximab plus hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine; sIL2R, soluble IL-2 receptor; TBLB, transbronchial lung biopsy; TRH, thyrotropin-releasing hormone; TSH, thyrotropin.

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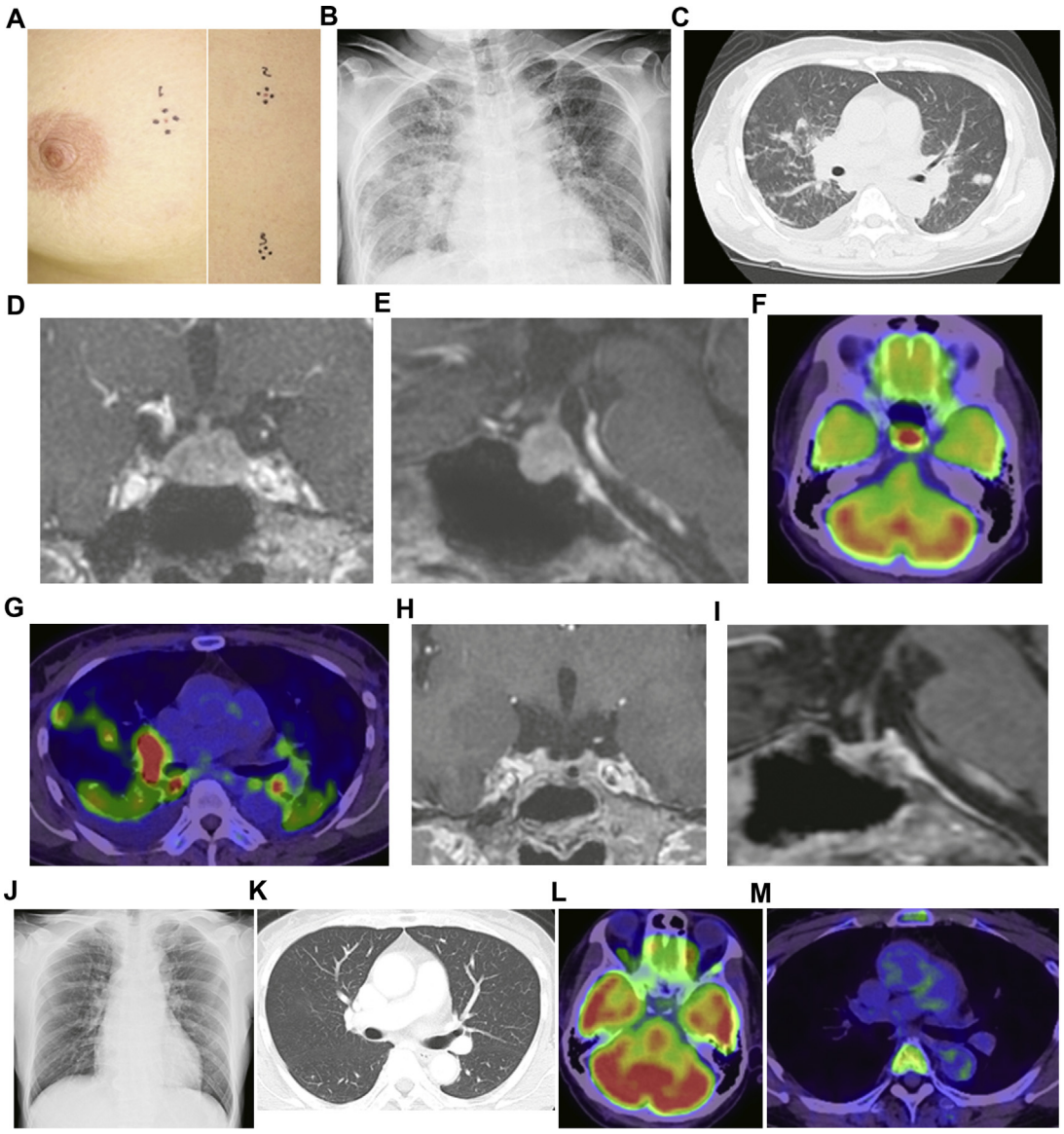

Fig. 1. Radiological images and skin findings on admission and after 1 course of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone). *A*, Five scattered erythema patches (marked by black dots) on the right breast and abdomen. *B*, Chest X-ray showing an infiltrative shadow. *C*, Chest enhanced computed tomography scan showing an infiltrative shadow, pleural effusion, and lymphadenopathy. *D*, *E*, Brain contrast-enhanced magnetic resonance imaging showing enlargement of the pituitary gland and pituitary stalk (*D*, coronal image and *E*, sagittal image). *F*, *G*, ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography images showing increased FDG uptake in the pituitary gland and lung. *H*, *I*, Brain enhanced magnetic resonance imaging showing disappearance of enlargement of the pituitary gland and pituitary stalk (*H*, coronal image and *I*, sagittal image). *J*, *K*, Chest X-ray and chest enhanced computed tomography scan showing the disappearance of infiltrative shadows, pleural effusion, and lymphadenopathy. *L*, *M*, FDG-positron emission tomography images showing no abnormal FDG uptake in the pituitary gland and lung.

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive type of B-cell lymphoma.[1] The disease is characterized by massive proliferation of large lymphoma cells within lumens of small and medium vessels in various organs. A definitive diagnosis requires histologic confirmation, and bone marrow biopsies and random skin biopsies are usually performed. The awareness of IVLBCL has improved since 2008 when the disease was listed as a rare subtype of diffuse large B-cell lymphoma in the World Health Organization classification.[1] IVLBCL usually occurs in older adults, and clinical characteristics have geographic differences. IVLBCL manifests nonspecific symptoms, such as fever, fatigue, and hypoxemia, and a wide variety of clinical signs as well as image findings associated with vascular obstruction in various organs, which make accurate diagnosis difficult. Treatment with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone) combined with an intrathecal infusion of methotrexate (MTX) is recommended for IVLBCL with central nervous system involvement. Although the reasons for intravascular localization of IVLBCL are unknown, it has been reported that the absence of intercellular adhesion molecule 1 (ICAM1) and β1 integrin (CD29) surface ligands may disable lymphoma cells from diapedesis across the endothelium.[2,3]

IVLBCL with pituitary involvement is rare. A literature search only identified 19 cases with morphologic or functional abnormalities in the pituitary gland. Furthermore, endocrinologic evaluation and detailed pathologic examination of the pituitary gland were performed in only a few cases. Here, we report a case of

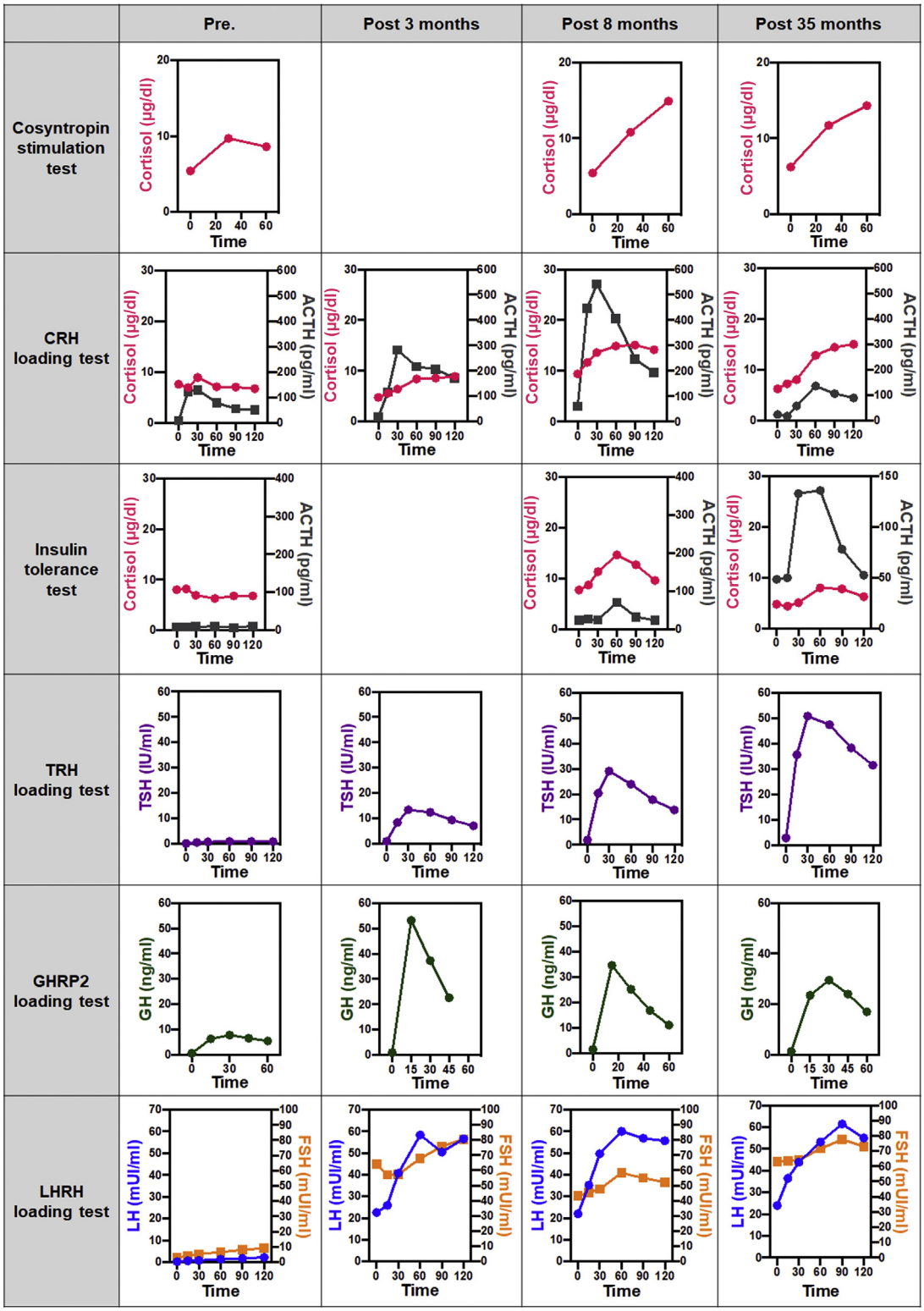

Fig. 2. Provocative pituitary tests before and after treatment. Transition of serum levels of anterior pituitary hormones in the cosyntropin stimulation test (250 μg, intravenous), CRH loading test (100 μg, intravenous), insulin tolerance test (0.05 U/kg, intravenous), TRH loading test (500 μg, intravenous), GHRP2 loading test (100 μg, intravenous), and LHRH loading test (100 μg, intravenous) before and after treatment (3 months, 8 months, and 35 months after admission). CRH, corticotropin-releasing hormone; GHRP2, growth hormone-releasing peptide 2; LHRH, luteinizing hormone-releasing hormone; TRH, thyrotropin-releasing hormone.

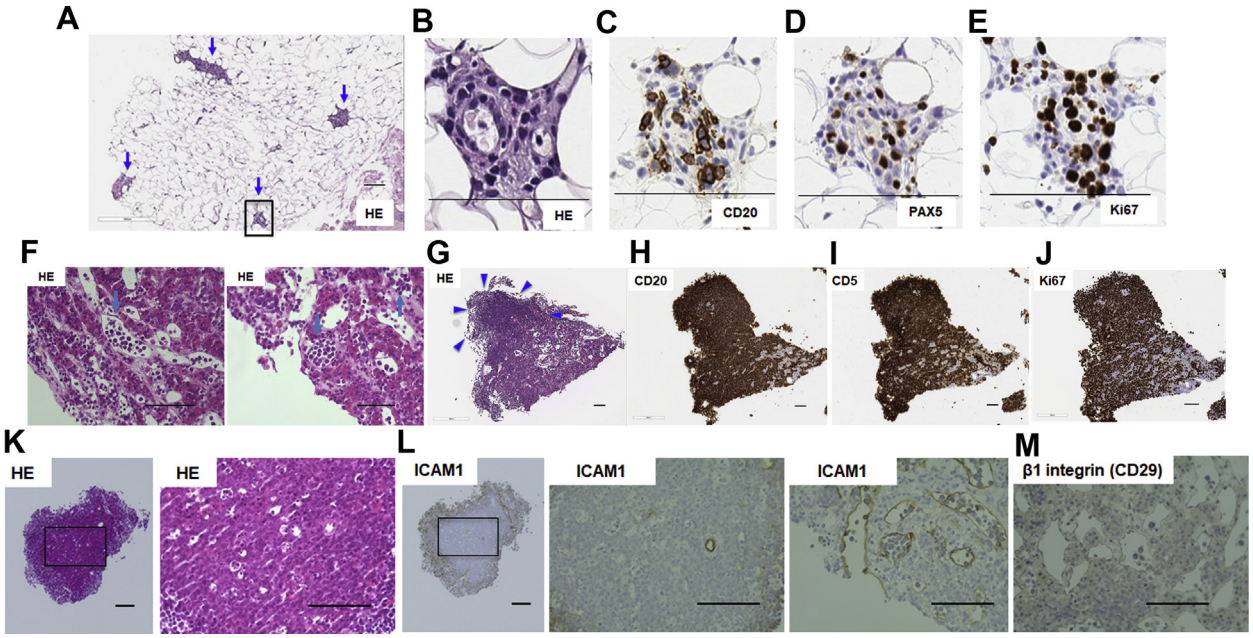

Fig. 3. Immunohistochemical analysis of skin biopsy and pituitary biopsy. *A*, Hematoxylin and eosin (HE) staining showing intravascular infiltration of atypical lymphoid cells in the skin (arrows). *B*, High magnification of the region enclosed by the rectangle in *A*. *C*, Positive immunoreactivity of CD20 in *B*. *D*, Positive immunoreactivity of paired box protein PAX5 in *B*. *E*, High expression of Ki67 in *B*. *F*, *G*, hematoxylin and eosin staining showing typical cell-rich infiltrate of lymphoma in pituitary gland tissue (arrowheads) and in small vessels (arrows). *H*, positive immunoreactivity of CD20 in *G*. *I*, Positive immunoreactivity of CD5 in *G*. *J*, High expression of Ki67 in *G*. *K*, *L*, HE staining and ICAM1 immunostaining of atypical lymphoid cells in small vessels and pituitary gland tissue. Note the strong reaction of the endothelial cells while the lymphoma cells are unstained. *M*, Positive β1 integrin (CD29) immunostaining of atypical lymphoid cells in small vessels and pituitary gland tissue. Scale bar: 100 μM.

ICAM1-negative IVLBCL with panhypopituitarism and pituitary enlargement that was diagnosed by pituitary biopsy and random skin biopsy. Based on the present case and literature review, we summarize the clinicopathological features of IVLBCL of the pituitary gland and discuss early detection and diagnosis of the disease.

Case Report

A 67-year-old Japanese woman was referred to our hospital with complaints of fever (39 °C) and generalized fatigue. At presentation, she had low blood pressure (BP 97/62 mm Hg) and tachypnea (respiration rate, 20/min). Physical examination revealed 5 scattered erythema patches on the body trunk that were without pain, tenderness, or telangiectasias (Fig. 1*A*) as well as bilateral coarse crackles in the lungs. Neurologic abnormalities were not observed. A chest radiograph demonstrated bilateral infiltrative shadows (Fig. 1*B*). A computed tomography scan confirmed the infiltrations together with pleural effusion and lymphadenopathy (Fig. 1*C*). Laboratory investigations revealed anemia (hemoglobin, 11.7 g/dL) and mild hyponatremia (sodium, 110 mEq/L) as well as elevated lactate dehydrogenase (LDH; 1500 IU/L) and soluble IL-2 receptor (sIL2R; 7075 U/L, normal range: 127-582 U/L) levels. Basal hormone analyses showed the following: adrenocorticotropic hormone (ACTH), 12 pg/mL (normal range: ≥46.0 pg/mL); cortisol, 7.4 μg/dL (normal range: 5-25 μg/dL); thyrotropin (TSH), 0.024 U/mL (normal range, 0.350-4.940 U/mL); free thyroxine, 0.63 ng/dL (normal range: 0.7-1.48 ng/dL); growth hormone (GH), 1.90 ng/mL (normal range: 0.04-3.60 ng/mL); insulin-like growth factor-1, 35 ng/mL (normal range: 60-180 ng/mL); luteinizing hormone (LH), 0.24 mIU/mL (normal range: 11-50 mIU/mL); follicle-stimulating hormone (FSH), 3.65 mUI/mL (normal range: 26-120 mIU/mL); estradiol, 31 pg/mL (normal range: ≤18 pg/mL); and prolactin, 20.64 ng/mL (normal range: 5.18-26.5 ng/mL). To assess the secretory reserve of anterior pituitary hormones, provocative tests were performed (Fig. 2). A low cortisol response in the cosyntropin stimulation test showed adrenal insufficiency. In addition, a normal ACTH response in the corticotropin-releasing hormone (CRH) loading test but not in the insulin tolerance test confirmed hypothalamic adrenal insufficiency (Fig. 2). Moreover, secondary hypothyroidism, GH deficiency, and hypogonadotropic hypogonadism were confirmed by the thyrotropin-releasing hormone (TRH) loading test, GH-releasing peptide 2 (GHRP2) loading test, and luteinizing hormone-releasing hormone (LHRH) loading test, respectively (Fig. 2). Severe GH deficiency was diagnosed (peak GH ≤ 9 ng/mL in the GH-releasing peptide 2 loading test), as previously reported.[4] Panhypopituitarism was diagnosed, and hydrocortisone and levothyroxine replacement was started. A large volume of dilute urine suggested diabetes insipidus but this was not observed before or after treatment. Subsequent contrast-enhanced magnetic resonance imaging studies demonstrated enlargement of the pituitary gland and pituitary stalk without evidence of adenoma (Fig. 1*D*, *E*). An ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography scan showed increased FDG uptake in the pituitary and lung lesions as well as bilateral hilar and mediastinal lymphadenopathy (Fig. 1*F*, *G*). Because IVLBCL was suspected due to rapid progression, several biopsies (random skin biopsies from both scattered erythema patches and normal-appearing skin, bone marrow biopsy, pituitary biopsy, and transbronchial lung biopsy [TBLB]) and bronchoalveolar lavage fluid (BAL) were simultaneously collected for pathologic and immunohistochemical analyses. Atypical lymphoid cells were found in blood vessels within the skin (Fig. 3*A*, *B*) and pituitary (Fig. 3*F*) but not in the bone marrow, TBLB, or BAL. In the skin biopsy, immunohistochemistry revealed that intravascular and neoplastic cells in the skin were positive for B-cell markers CD20 and paired box protein PAX5 (Fig. 3*C*, *D*) and comprised 10% Ki67-positive cells (Fig. 3*E*). In the pituitary biopsy, aggregation of large lymphoid cells was found not only inside blood vessels but also in pituitary tissue (Fig. 3*F*, *G*), and the cells were positive for B-cell

Table 1
Case Reports of Intravascular Large B-cell Lymphoma with Pituitary Involvement

Author (year)	Case	Brain imaging	Hormone deficits	Diagnostic biopsy site	Chemotherapy	Outcome	Follow-up duration
Our case	67, F	Enlarged pituitary gland and pituitary stalk	LH, FSH, GH, TSH, ACTH, cortisol	Pituitary and random skin	R-CHOP with intrathecal MTX	Alive	39 months
Simeni et al (2019) [6]	48, F	Enlarged pituitary gland and pituitary stalk; left pre-Rolandic lesion; medial medullary lesion	LH, FSH, TSH	Spleen	R-CHOP with intrathecal MTX	Dead	2 months
Hussain et al (2018) [7]	47, F	Pituitary mass	TSH, cortisol (partial anterior hypopituitarism)	Adrenal gland	R-CHOP with intrathecal MTX	Alive	12 months
Pattison et al (2016) [8]	58, M	Pituitary mass	Panhypopituitarism (details unknown)	Pituitary	R-CHOP	Alive	68 months
	63, M	Focal pituitary FDG uptake	Not analyzed	Bone marrow	R-CHOP	Alive	31 months
Sawada et al (2016) [9]	71, F	Normal	LH, FSH, TSH, ACTH	Bone marrow, random skin, and spinal fluid	R-CHOP with intrathecal MTX	Alive	114 days
Akhtar et al (2013) [10]	75, M	Normal	LH, FSH, GH, TSH, SIADH	Not done	Not done	Dead	2 weeks
Anila, et al (2012) [11]	68, F	Pituitary mass	LH, FSH, TSH, cortisol	Pituitary	Not done	Dead	…
Rizek, et al (2012) [12]	68, M	Pituitary mass	LH, FSH, TSH, cortisol	Pituitary and nasal polyp	R-CHOP	Alive	6 months
Yasuda et al (2010) [13]	69, F	Pituitary mass	LH, FSH, TSH, ACTH	Breast tumor	R-CHOP	Alive	3 years
Pekic, et al (2008) [14]	67, F	Partial empty sellar	TSH, ACTH, GH	Bone marrow	R-CHOP	Alive	18 months
Svajdler, M., et al (2006) [15]	63, F	Normal	LH, FSH, TSH, ACTH	Autopsy	Not done	Dead	3 months
Price et al (2002) [16]	57, F	Details unknown	Hypopituitarism (details unknown)	Details unknown	Details unknown	Dead	…
Schleinitz et al (2002) [17]	76, M	Pituitary mass	Details unknown	Details unknown	Details unknown	Dead	…
Kraus et al (1999) [18]	59, F	Normal	LH, FSH, TSH	Autopsy	Not done	Dead	…
	68, M	Normal	LH, FSH, TSH, ACTH	Autopsy	Not done	Dead	…
Demirer, et al (1994) [19]	77, F	Normal	Panhypopituitarism (details unknown)	Lip	CHOP	Dead	…
Smadja et al (1991) [20]	63, F	Normal	Hypopituitarism (details unknown)	Autopsy	Not done	Dead	2.5 months
Domizio et al (1989) [21]	58, F	Pituitary mass	Panhypopituitarism (details unknown)	Autopsy	Not done	Dead	…
Wick et al (1986) [5]	62, M	Pituitary mass	Hypopituitarism (details unknown)	Autopsy	Not done	Dead	…

Abbreviations: ACTH = adrenocorticotropic hormone; F = female; FDG =18F-fluorodeoxyglucose; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; M = male; MTX = methotrexate; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone; SIADH = syndrome of inappropriate antidiuretic hormone secretion; TSH = thyrotropin.

marker CD20 (Fig. 3*H*) and B1-cell/T-cell marker CD5 (Fig. 3*I*) and had an extremely high Ki67-positive rate of 90% (Fig. 3*J*). Decreased staining for ACTH, TSH, GH, and FSH was confirmed at the lymphoma infiltration sites of the pituitary gland. Intriguingly, the lymphoma cells were negative for ICAM1, although the endothelial cells were strongly positive (Fig. 3*K*, *L*). On the other hand, atypical lymphoid cells in small vessels and pituitary gland tissue were positive for β1 integrin (CD29) (Fig. 3*M*). On day 19 after admission, the final diagnosis of IVLBCL with pituitary infiltration was made. The patient was initially treated with R-CHOP and subsequently switched to R-hyper-CVAD/MA (rituximab plus hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine) combined with intrathecal MTX infusions, followed by autologous stem cell transplantation with MEAM (ranimustine, etoposide, cytarabine, and melphalan) conditioning. The patient's fever subsided immediately, and LDH and sIL2R levels were normalized after starting R-hyper-CVAD/MA. Moreover, the enlarged pituitary gland and stalk were reduced (Fig. 1*H*, *I*), the infiltrative lung shadows with pleural effusion and lymphadenopathy were resolved (Fig. 1*J*, *K*), and abnormal FDG uptake in the pituitary gland and lung vanished (Fig. 1*L*, *M*) after R-hyper-CVAD/MA. Reevaluation of the hormonal status using several provocative tests at 3, 8, and 35 months after admission showed that the levels of TSH, GH, LH, and FSH had returned to normal after 3 months, and ACTH was normalized after 8 months (Fig. 2). Levothyroxine replacement was stopped after 8 months and hydrocortisone after 35 months. The patient remained in complete remission at 42 months after autologous stem cell transplantation.

Ethics Approval and Consent to Participate

This study was approved by the Human Research Ethics Committee at Chiba University (approval number: 3653). Informed consent was obtained from the patient before undergoing all clinical procedures.

Consent for Publication

Consent for publication was obtained from the patient.

Discussion

Hypopituitarism associated with IVLBCL was firstly described in 1986.[5] Only 19 cases of IVLBCL involving the pituitary gland with morphologic or functional abnormalities in the pituitary gland have been reported to date. The clinical and endocrinological features of the reported cases, including our case, are summarized in Table 1.[5-21] The patients with pituitary involvement were

predominantly women (13/20, 65%). The ages of the patients ranged from 47 to 77 years, with a mean age of 64 years. Thirteen cases were reported from Europe, 3 from Asia, and 4 from the United States. Brain imaging revealed enlargement of the pituitary gland and stalk in 2 cases, a pituitary mass in 8 cases, and a normal pituitary in 7 cases. The patients presented with persistent fever of unknown origin (8 cases), fatigue (4 cases), neurologic signs (2 cases), or edema (2 cases). Almost all cases had multiple pituitary disorders judged by basal hormone levels. Only 3 cases, including ours, underwent the provocative pituitary tests before and after treatment. It has been reported that the majority of IVLBCL patients are diagnosed by random skin biopsy followed by bone marrow biopsy. Among the cases of IVLBCL with pituitary involvement, 6 cases were diagnosed post mortem by autopsy, particularly before 2006. From the 10 patients who underwent tissue biopsy, 4 biopsies from the pituitary gland, 2 from random skin, 3 from bone marrow, and 1 each from the spleen, adrenal gland, breast, and lip were collected. All 4 biopsies from the pituitary gland were stained with hematoxylin and eosin and immunostained with CD20. Nine patients were treated with R-CHOP with or without intrathecal MTX and 1 patient with CHOP. The fact that 8 of 10 treated patients were alive suggested that IVLBCL of the pituitary gland was treatable.

In this study, we report a Japanese case of ICAM1-negative IVLBCL in the pituitary gland with reversible hypopituitarism using detailed pathologic investigations of skin and pituitary biopsy tissue. Skin biopsy revealed a proliferation of atypical lymphocytes within the blood vessels, resulting in a clinical diagnosis of IVLBCL. Characteristic features of IVLBCL include persistent fever, decreased performance status, hypoxemia, impaired consciousness, and markedly elevated LDH and sIL2R levels. In addition to these typical symptoms, hypotension and hyponatremia as well as increasing FDG uptake in the pituitary gland suggest pituitary involvement in our case. To the best of our knowledge, this is the first report of IVLBCL involving the pituitary gland with neoplastic lymphocytes proven to be ICAM1-negative. Lack of ICAM1 expression may partially explain the propensity for localization of lymphoma cells in the lumen of blood vessels.[2,3] Anatomically, the pituitary gland does not have a blood-brain barrier and receives abundant blood flow. These anatomical features of the pituitary gland suggest that in advanced IVLBCL, intravascularly localized ICAM1-negative lymphoid cells extravasate into the pituitary tissue, leading to panhypopituitarism. The proliferation grade of IVLBCL appears to vary in different tissues: lymphocytes remaining inside blood vessels in the skin showed a Ki67 index of 10%, whereas lymphocytes that invaded the pituitary gland showed a Ki67 index of 90%. Murase et al[22] demonstrated that de novo $CD5^+$ diffuse large B-cell lymphoma might constitute a distinct subtype with an aggressive clinical course, and $CD5^+$ lymphoma cells were found in the pituitary biopsy of our case. Although no atypical lymphocytes were detected from the TBLB and BAL, the lungs also seemed to be involved because lung pathology improved immediately after R-CHOP therapy.

Conclusion

VLBCL with pituitary involvement can be successfully treated by hormone replacement therapy and subsequent immunochemotherapy. Therefore, early recognition of the clinicopathological features is necessary to prevent mortality.

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Author Contributions

All authors diagnosed or treated the patient. T.T. and S.S. contributed to the study conception and design. Data collection and analysis were performed by K.N. and S.S. K.H. and Y.I. performed the pituitary biopsy. N.I. and J-I.I. performed the pathologic analysis. The first draft of the manuscript was written by S.S., and C.O., E.S., I.T., and K.Y. commented and developed the idea. All authors read and approved the final manuscript.

Disclosure

The authors have no multiplicity of interest to disclose.

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