Case Report

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

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A B S T R A C T

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.

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Abbreviations: ACTH, adrenocorticotropic hormone; BAL, bronchoalveolar lavage fluid analysis; CRH, corticotropin-releasing hormone; FDG, 18F-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 hyperfractionated 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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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 B1 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. 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, 18F-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.
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.
ICAM-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. 1A) as well as bilateral coarse crackles in the lungs. Neurologic abnormalities were not observed. A chest radiograph demonstrated bilateral infiltrative shadows (Fig. 1B). A computed tomography scan confirmed the infiltrations together with pleural effusion and lymphadenopathy (Fig. 1C). 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) levels. Basal hormone analyses showed the following: adrenocorticotropic hormone (ACTH), 22 pg/mL (normal range: 5.18-26.5 pg/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. 1D, E). An 18F-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. 1F, 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. 3A, B) and pituitary (Fig. 3F) 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. 3C, D) and comprised 10% Ki67-positive cells (Fig. 3E). In the pituitary biopsy, aggregation of large lymphoid cells was found not only inside blood vessels but also in pituitary tissue (Fig. 3F, G), and the cells were positive for B-cell
marker CD20 (Fig. 3H) and B1-cell/T-cell marker CD5 (Fig. 3I) and had an extremely high Ki67-positive rate of 90% (Fig. 3J). 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. 3K, L). On the other hand, atypical lymphoid cells in small vessels and pituitary gland tissue were positive for β1 integrin (CD29) (Fig. 3K). On day 19 after admission, the final diagnosis of IVLBCI 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, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) 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. 1H, I), the infiltrative lung shadows with pleural effusion and lymphadenopathy were resolved (Fig. 1J, K), and abnormal FDG uptake in the pituitary gland and lung vanished (Fig. 1L, 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 IVLBCI was firstly described in 1986. Only 19 cases of IVLBCI 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. The patients with pituitary involvement were
lymphoma might constitute a distinct subtype with an aggressive therapy. 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., 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.

References

1. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117:5019–5032.
2. Orvat DE, Batalis NL. Intravascular large B-cell lymphoma. Arch Pathol Lab Med. 2012;136:331–338.
3. Ponzo M, Arrigoni G, Gozzi VE, Del Corso B, Maggioni M, Scapinellino A, et al. Lack of CD 29 (beta1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Hum Pathol. 2000;31:220–226.
4. Chihara K, Shimatsu A, Hizuka N, Tanaka T, Seino Y, Katoh Y. A single diagnostic test using GH-releasing peptide-2 in adult GH deficiency. Eur J Endocrinol. 2007;157:19–27.
5. Wick MR, Mills SE, Scheithauer BW, Cooper KO, Devitt MA, Parkinson K. Reassessment of malignant "angioendotheliomatosis." Evidence in favor of its reclassification as "intravascular lymphomatosis.". Am J Surg Pathol. 1986;10:112–123.
6. Simeun Njonnou SR, Couturier B, Gombeir V, Verbanck S, Devuyst F, El Hachem G, et al. Pituitary gland and neurological involvement in a case of hemophagocytic syndrome revealing an intravascular large B-cell lymphoma. Case Rep Hematol. 2019;2019:9625075.
7. Hussain S, Hallam S, Beltran L, Hareon A, Majumdar K, Shamash J, et al. Intravascular large B-cell lymphoma presenting as a pituitary mass with bilateral adenal enlargement and haemophagocytic lymphohistiocytosis. Br J Haematol. 2018;181:851–852.
8. Patterson DA, Hofman MS, Bazargan A, Colman P, Hicks R. Intense focal pituitary FDG uptake due to intravascular large B-cell lymphoma in pyrexia of unknown origin. Am J Hematol. 2016;91:1167–1168.
9. Sawada Y, Ishii S, Koga Y, Tomizawa T, Matsui A, Tomaru T, et al. Reversible hypopituitarism associated with intravascular large B-Cell lymphoma: case report of successful immunochemotherapy. Tohoku J Exp Med. 2016;238:197–203.
10. Akihar S, Cheesman E, Jude EB. SIADH and partial hypopituitarism in a patient with intravascular large B-cell lymphoma: a rare case of a common presentation. BMJ Case Rep. 2013;2013, bcr2012007147.
11. Anila KR, Nair RA, Koshy SM, Jacob PM. Primary intravascular large B-cell lymphoma of the pituitary. Indian J Pathol Microbiol. 2012;55:549–551.
12. Rizek P, Seidlach M, Altrukstani M, Leung A, Fraser JA. Sellar and parasellar intravascular lymphoma mimicking pituitary apoplexy. J Neuropathol Immunol. 2012;32:33–37.
13. Yasuda M, Akiyama M, Miyamoto S, Watarai M, Takahama Y, Kitamura M, et al. Primary sellar lymphoma: intravascular large B-cell lymphoma diagnosed as a double cancer and improved with chemotherapy, and literature review of primary parasellar lymphoma. Pituitary. 2010;1:39–47.
14. Pelcik S, Miletic S, Colovos N, Colovos M, Popovic V. Intravascular large B-cell lymphoma as a cause of hypopituitarism: gradual and late reversal of hypothalamic-pituitary dysfunction. Blood. 2008;34:11–16.
15. Sivanjdeger M, Lazutino I, Bohn P, Palmo M. Intravascular variant of diffuse large B-cell lymphoma with combined endocrine involvement. Wien Klin Wochenschr. 2006;118:422–425.
16. Price DA, Thaker H, James A, Snow MH. Hypopituitarism in a patient with intravascular lymphomatosis. Haematologica. 2002;87:ECR36.
17. Schleinitz N, Birnst E, Mazodier K, Charbonnier A, Horchowski N, Andrac-Meyer L, et al. Two cases of intravascular lymphomatosis disclosing with hypopituitarism. Haematologica. 2002;87:ECR21.
18. Kraus MD, Jones D, Bartlett NL. Intravascular lymphoma associated with endocrine dysfunction: a report of four cases and a review of the literature. Am J Med. 1999;107:169–176.
19. Demirer T, Dail DH, Aboulaafer DM. Four varied cases of intravascular lymphomatosis and a literature review. Cancer. 1994;73:1738–1745.
20. Smadja D, Mas JL, Fallet-Bianco C, Meyniard O, Sicard D, de Recondo J, et al. Intravascular lymphomatosis (neoplastic angioendotheliosis) of the central nervous system: case report and literature review. *Journal Neurooncol.* 1991;11:171–180.

21. Domizio P, Hall PA, Cotter F, Amiel S, Tucker J, Besser GM, et al. Angiotropic large cell lymphoma (ALCL): morphological, immunohistochemical and genotypic studies with analysis of previous reports. *Hematol Oncol.* 1989;7:195–206.

22. Murase T, Yamaguchi M, Suzuki R, Okamoto M, Sato Y, Tamaru J, et al. Intravascular large B-cell lymphoma (IVLBCLI): a clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. *Blood.* 2007;109:478–485.