

Case Report

Intravascular large B-cell lymphoma presenting with decreased brain uptake on ¹⁸F-fluorodeoxyglucose positron emission tomography: a case report and literature review

Toshiya Maebayashi¹, Naoya Ishibashi¹, Takuya Aizawa¹, Masakuni Sakaguchi¹, Homma Taku², Kura Yoshimasa³, Toshirou Takimoto⁴, Yoshiaki Tanaka⁵

¹Department of Radiology, Nihon University School of Medicine, Itabashi-ku, Tokyo 173-8610, Japan; ²Department of Human Pathology, Division of Pathology and Microbiology, Nihon University School of Medicine, Itabashi-ku, Tokyo 173-8610, Japan; ³Department of Hematology, Kasukabe Medical Center, Kasukabe, Saitama 344-8588, Japan; ⁴Department of Pathology, Kasukabe Medical Center, Kasukabe, Saitama 344-8588, Japan; ⁵Department of Radiation Oncology, Kawasaki Saiwai Hospital, Kawasaki, Kanagawa 212-0014, Japan

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Abstract: Intravascular large B-cell lymphoma (IVLBCL) is a rare disease characterized by proliferation of lymphoma cells in small vessels. Unlike typical lymphoma, this disease does not cause lymphadenopathy, instead presenting with a wide range of symptoms. It is thus difficult to diagnose such cases, often delaying treatment. ¹⁸F-Fluorodeoxyglucose positron emission tomography (PET) is useful for diagnosing IVLBCL. Herein, this study describes a IVLBCL case presenting with decreased brain uptake, i.e. a so-called superscan on PET. The patient was a 60-year-old man who had experienced fevers and lower limb edema for 1 month. A blood test at his first visit revealed pancytopenia. A PET scan was performed for detailed examination. Pathological uptakes were observed in the bone marrow, liver and spleen. However, there was little uptake in the brain. Although IVLBCL was suspected, random skin biopsies revealed no abnormalities. Therefore, a liver biopsy was performed, which confirmed IVLBCL. Six cycles of R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, and oncovin) have been administered, to date, resulting in resolution of the pancytopenia. He has remained alive without recurrence for 13 months since the diagnosis of IVLBCL. In conclusion, patients with IVLBCL, which is characterized by proliferation of lymphoma cells in small vessels, may present with PET superscan findings, which may indicate a missed opportunity to treat the disease. However, PET superscan findings may also reflect a refractory pathological condition.

Keywords: Intravascular large B-cell lymphoma, positron emission tomography, superscan

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare disease characterized by proliferation of lymphoma cells in small vessels [1, 2]. Unlike typical lymphoma, this disease does not cause lymphadenopathy, instead presenting with various symptoms, such as skin findings related to tumor thrombus, hepatosplenomegaly, respiratory symptoms, and neurological symptoms [3]. Consequently, it is difficult to diagnose, treatment is often delayed, and outcomes are generally poor. Positron emission tomography (PET), which allows whole-body scans, is there-

fore considered to be useful for diagnosing and managing this malignancy [4-7]. In addition, IVLBCL appears to be a systemic disease, as its pathology is characterized by intravascular lesions. Thus, under normal circumstances, PET should show the most intense uptake in the brain. Due to the pathology of IVLBCL, however, radiotracers are sometimes absorbed systemically, such that the disease may present indirectly with decreased brain uptake, i.e. so-called superscan findings. During management of the patient described herein, showing decreased brain uptake on PET, previously reported cases were reviewed to assess the



Figure 1. Maximum-intensity projection image of whole-body ^{18}F -fluorodeoxyglucose positron emission tomography scan before treatment. Brain uptake was low, and abnormal uptakes were observed in the bone marrow, liver, spleen, and the left pulmonary hilum. The findings are consistent with a so-called superscan. A liver biopsy performed after this PET scan yielded a diagnosis of intravascular large B-cell lymphoma.

significance of decreased brain uptake on PET in IVLBCL. This is the first report, to our knowledge, describing therapeutic effects in an IVLBCL case presenting with decreased brain uptake on PET.

Case report

A 60-year-old man presented with a 1-month history of fever and lower limb edema. He was referred to our department for detailed examination and treatment. His medical history was

otherwise unremarkable, and he had previously been healthy. A blood test at his first visit revealed pancytopenia.

The laboratory findings on admission included white blood cell count 1,800/mL, hemoglobin 12.0 g/dL, and platelet count 2.0×10^4 /mL. The soluble interleukin-2 receptor level was high at 14,500 U/mL. Blood coagulation parameters were also elevated.

His consciousness level and his motor and cognitive functions were normal. An alcohol-related disorder was indicated by clinical findings. A lung tumor was also suspected. An ^{18}F -fluorodeoxyglucose PET scan was performed for staging, and pathological uptakes were noted in the bone marrow, liver and spleen. However, there was little uptake in the brain (**Figure 1**). Because IVLBCL was suspected, superficial lymph nodes were examined but no definite abnormalities were detected. No skin lesions were observed, nor did random skin biopsies indicate any abnormalities. Therefore, a liver biopsy was performed for further examination and yielded a diagnosis of IVLBCL (**Figure 2A-F**). Bone marrow aspiration and biopsy revealed bone marrow hyperplasia, but no clear invasion of lymphoma cells into the bone marrow was observed. These images may represent conspicuously enhanced bone marrow function due to pancytopenia induced by rapid exacerbation of the lesions and enhanced splenic function and may even involve splenic infiltration. R-CHOP therapy (cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and rituximab 375 mg/m² on day 1, and oral prednisolone 40 mg/m² on days 1-5) was initiated after the diagnosis had been confirmed, and the patient's symptoms as well as blood test findings improved in response to this regimen. Six cycles of R-CHOP therapy have been administered, to date, and PET currently shows no abnormal findings in the brain (**Figure 3**). However, a PET scan showed increased uptake in the left hilum of the lung. A tumor biopsy was performed for further examination and yielded a diagnosis of small cell lung cancer. He received chemoradiotherapy and a good therapeutic effect was obtained.

It was possible to initiate chemotherapy in this case based on the early diagnosis. He has remained alive without recurrence for 16 months, to date, since the diagnosis of IVLBCL.

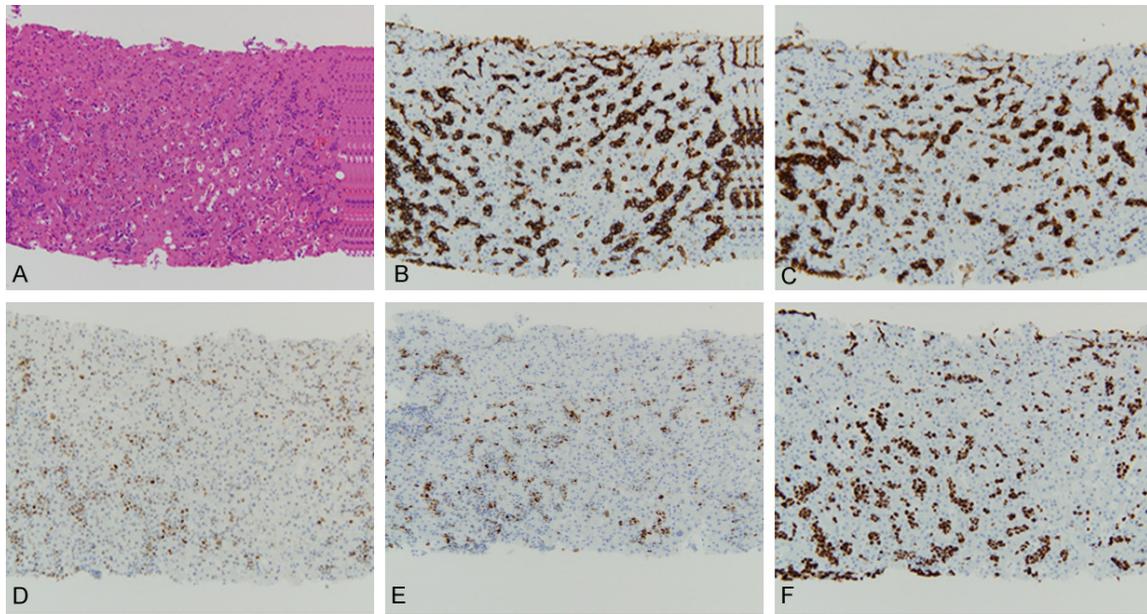


Figure 2. Pathological findings Hematoxylin and eosin staining reveals infiltration of large atypical lymphocytes into hepatic vessels (A). Immunostaining revealed the specimen to be diffusely positive for B-cell markers CD20 (B), CD79a (C), bcl-6 (D), and MUM1 (E). The tumor cells located in the vessels were positive for Ki-67 (F), a nuclear antigen expressed intracellularly during cell cycle progression from the G1 to M phases. Based on these findings, intravascular large B-cell lymphoma was diagnosed.

Discussion

IVLBCL is a rare subtype of extranodal lymphoma [1, 2]. It is classified into the classical type predominantly characterized by skin and central nervous system lesions; the Asia subtype characterized by multi-visceral lesions (e.g., hemophagocytic syndrome, bone-marrow lesions, and hepatosplenomegaly); and the solitary cutaneous subtype localized to the skin [8]. As our patient presented with pancytopenia and hepatosplenomegaly, the Asia subtype, as reported by Murase et al. [8], was diagnosed.

The primary site of IVLBCL is small vessels, and a variety of clinical findings have been reported; therefore, this disease is difficult to diagnose. Due to the possibly wide range of clinical findings at presentation, PET is useful, as it allows whole-body scans [4-7]. IVLBCL has been reported to commonly occur in the lungs, bone marrow, spleen, liver, and adrenal glands [9]. However, because this tumor is very small, pathological uptake may need to be differentiated from reactive uptake or that resulting from enhanced bone marrow function, particularly in patients with diffuse uptake in tumors and

those, such as our case, with pancytopenia due to enhanced splenic function [10]. In this case, decreased brain uptake on PET, which showed improvement after chemotherapy, appears to be an indirect finding as he had no central nervous system symptoms prior to treatment. In cases showing various clinical findings but no tumors, decreased brain uptake appears to be a specific finding based on the pathology of IVLBCL. Thus, a search of the literature was performed for past reports describing PET images. The search using “intravascular large cell lymphoma” and “PET” in PubMed yielded 37 reports, of which 22 included images of the brain [4-7, 9, 11-27]. Furthermore, images from 6 of these 22 reports showed decreased brain uptake [22-27]. Prathamesh et al. indicated that the decreased brain uptake is attributable to brain hypometabolism [27]. However, in our view, in patients without psychiatric symptoms, such as our present case, brain uptake is an indirect consequence of high systemic uptake rather than being due to brain hypometabolism. A related finding is that 2 reported IVLBCL patients had cerebral microinfarctions which had resulted from intravascular lesions caused by the IVLBCL [28, 29]. However, in our patient,



Figure 3. Maximum-intensity projection image of whole-body ^{18}F -fluorodeoxyglucose positron emission tomography after chemotherapy. Brain uptake was normalized. The abnormal uptakes in the liver and spleen also showed normalization following chemotherapy.

PET scans revealed no evidence of either cerebral infarction or brain hypometabolism.

Of the 22 reports reviewed, 14 (17 patients) described outcomes and therapeutic effects [4-7, 13-19, 22-24]. Of all 18 patients, including ours, 5 (27.7%) showed decreased brain uptake [22-24] and 13 (72.2%) showed normal brain uptake on PET [4-7, 13-19] (Table 1).

Regarding outcomes, the 5 patients who showed decreased brain uptake included 1 who could not be treated due to poor condition [24] and 2 who died within 2 weeks after treatment initiation [23]. While 1 reported patient showed prolonged survival, the decreased brain uptake observed in this patient might have been related to long-term diabetes mellitus [22]. Of the 13 patients with normal brain uptake on PET, 8 lived without relapse [4-6, 14-16, 18, 19] whereas 5 showed disease relapse or died [6, 7, 13, 17]. Although we cannot draw a definitive conclusion, due to the small sample size, IVLBCL showing decreased brain uptake on PET may be refractory and the prognosis appears to be poor. Therefore, when IVLBCL is diagnosed based on clinical features and decreased brain uptake is observed on PET, it might be advisable to start chemotherapy based on early diagnosis. In conclusion, in patients with IVLBCL, PET superscan findings may indicate a missed opportunity to have treated this disease earlier or that IVLBCL is a refractory pathological condition. It is hoped that further cases can be accumulated and investigated for both therapeutic effects and outcomes of IVLBCL.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Toshiya Maebayashi, Department of Radiology, Nihon University School of Medicine, 30-1 Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan. Tel: +81 339728111 Ext. 8328; Fax: +81 339582454; E-mail: maebayashi.toshiya@nihon-u.ac.jp

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Table 1. Twenty-two reports on intravascular large B-cell lymphoma included maximum-intensity projection images of whole-body ¹⁸F-fluorodeoxyglucose positron emission tomography scans. The presence or absence of brain uptake, age, sex, outcome, and therapeutic strategies, among other parameters, are listed in the table

Year reported	Authors	Age (years)	Sex	Presence of brain uptake on PET	Outcome	Therapeutic strategies
2018	Our case	60	Male	No	Residual lesions on PET (Partial response)	6 cycles of R-CHOP
2016	Li et al. [14]	61	Female	No (History of diabetes mellitus)	35 months disease free follow up	None
2008	Shimada et al. [23]	69	Female	No	Death due to the disease 11 days	PSL
		76	Male	No	Death due to the disease 14 days	PSL and CPA+Dex
2013	Joshi et al. [24]	61	Male	No	Before receiving any definitive treatment, the patient expired.	None
2012	Oh et al. [25]	64	Male	No	None (Good response)	3 cycles of R-CHOP
2007	Odawara et al. [26]	73	Female	No	None (Good response)	2 cycles of R+1 cycle of CHOP
2010	Sanli et al. [27]	61	Female	No	None	None
2008	Hoshino et al. [4]	70	Female	Yes	4 months disease free follow up	6 cycles of CHOP
2012	Takahashi et al. [5]	76	Male	Yes	8 months disease free follow up	8 cycles of R+6 cycle of THP-COP
2015	Yamada et al. [6]	65	Male	Yes	Death due to the disease 7 months	PSL and whole brain irradiation
		46	Male	Yes	5 months disease free follow up	7 cycles of R-CHOP and whole brain irradiation
2011	Matsue et al. [7]	74	Male	Yes	Death due to the disease 4 months	3 cycles of R-CHOP+ MTX
		84	Female	Yes	Recurrence 5 months later	7 cycles of R-CHOP+MTX
2010	Wagner T et al. [9]	71	Female	Yes	None (Partial response)	2 cycles of R-CHOP
2012	Takehige et al. [11]	62	Male	Yes	None (Good response)	8 cycles of R-CHOP
2017	Shiiba et al. [12]	53	Female	Yes	None (Good response)	6 cycles of R-CHOP+MTX+2 cycles of R
2011	Kawai et al. [13]	69	Male	Yes	Death due to the disease 6 months	1 cycle of MTX-CHOP and 3 cycles of R-CHOP+MTX.
2012	Bai et al. [14]	41	Female	Yes	9 months disease free follow up	CHOP and radiation
2011	Yamashita et al. [15]	66	Male	Yes	33 months disease free follow up	8 cycles of R-CHOP
2012	Boslooper et al. [16]	67	Male	Yes	7 months disease free follow up	6 cycles of R-CHOP and intrathecal MTX
2010	Hofman et al. [17]	50	Female	Yes	Recurrence 3 months after transplantation	8 cycles of R-CEOP and Transplantation
2007	Nakazato et al. [18]	84	Male	Yes	15 months disease free follow up	8 cycles of R-CHOP
2004	Colavolpe et al. [19]	71	Male	Yes	16 months disease free follow up	4 cycles of R-MCVP and Transplantation
2010	Kohan et al. [20]	71	Male	Yes	None	None
2013	Miura et al. [21]	39	Female	Yes	None	None

Abbreviations: PET: positron emission tomography; PSL: Prednisolone; Dex: Dexamethasone; R: Rituximab; MTX: methotrexate; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CEOP: cyclophosphamide, etoposide, vincristine and prednisone; MCVP: methotrexate, cyclophosphamide, etoposide and prednisone.

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