



# Intravascular large B-cell lymphoma as a recurrence of primary central nervous system lymphoma after chemotherapy: A case report

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## ABSTRACT

We report about a 48-year-old woman diagnosed with primary central nervous system lymphoma (PCNSL). After chemotherapy and autologous stem cell transplantation, she presented with a continuous high-grade fever. Positron emission tomography-computed tomography revealed prominent hepatosplenomegaly and high diffuse uptake of 18F-fluorodeoxyglucose in the liver, spleen, and lungs. Intravascular large B-cell lymphoma (IVLBCL) was diagnosed using random skin biopsy. There were no symptoms of IVLBCL at the time of diagnosis of PCNSL. The histopathological features of PCNSL and IVLBCL were nearly similar. These findings suggest that IVLBCL was the recurrence of PCNSL rather than a separate entity.

## 1. Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare diffuse large B-cell lymphoma (DLBCL) characterized by selective growth of malignant lymphocytes within the lumina of small vessels of various organs. Most patients with IVLBCL present with various symptoms, including B symptoms, and central nervous system (CNS) and cutaneous symptoms. Because of the absence of a diagnostic algorithm for IVLBCL, nearly half of the patients used to be diagnosed only after autopsy. The clinical features of IVLBCL are currently recognized more widely, although approximately 20% of patients are still diagnosed postmortem [1].

IVLBCL can present as a recurrence of other DLBCLs; however, to the best of our knowledge, there are no reports of IVLBCL presenting as a recurrence of primary CNS lymphoma (PCNSL). Herein, we reported about a patient who was diagnosed with PCNSL and who later relapsed with IVLBCL.

## 2. Case presentation

A 48-year-old woman consulted our hospital for headache. She had a history of breast cancer that was treated with chemotherapy and anti-HER2 antibodies. Brain magnetic resonance imaging (MRI) revealed a mass in the right temporal lobe (Fig. 1a). Biopsy was performed

immediately, and because breast cancer metastasis was suspected, radiotherapy was initiated. However, after she received 21 Gy of radiotherapy, the final histological diagnosis was PCNSL with diffuse infiltration of large lymphoid cells in the cerebrum, particularly with perivascular infiltration (Fig. 2a) [2]. On immunohistochemistry, the large lymphoid cells were positive for CD5, CD20, BCL2, BCL6, and MUM1 and negative for CD3, CD10, cyclinD1, EBER, SOX1, and LEF1. The Ki-67 labeling index was approximately 90%, and the c-myc protein was observed in approximately 50% of tumor cells. There was no break of *MYC* and *CCND1* on fluorescent in situ hybridization. G-Banding could not be performed. Positron emission tomography-computed tomography (PET-CT) showed no abnormal uptake of <sup>18</sup>F-fluorodeoxyglucose (FDG) (Fig. 1b). No evidence of bone marrow involvement was revealed during initial bone marrow biopsy. Therefore, PCNSL was diagnosed. Radiotherapy was discontinued, and chemotherapy was initiated. After the administration of six cycles of high-dose methotrexate (HD-MTX) (3.5 g/m<sup>2</sup>), complete remission was achieved (Fig. 1c, d).

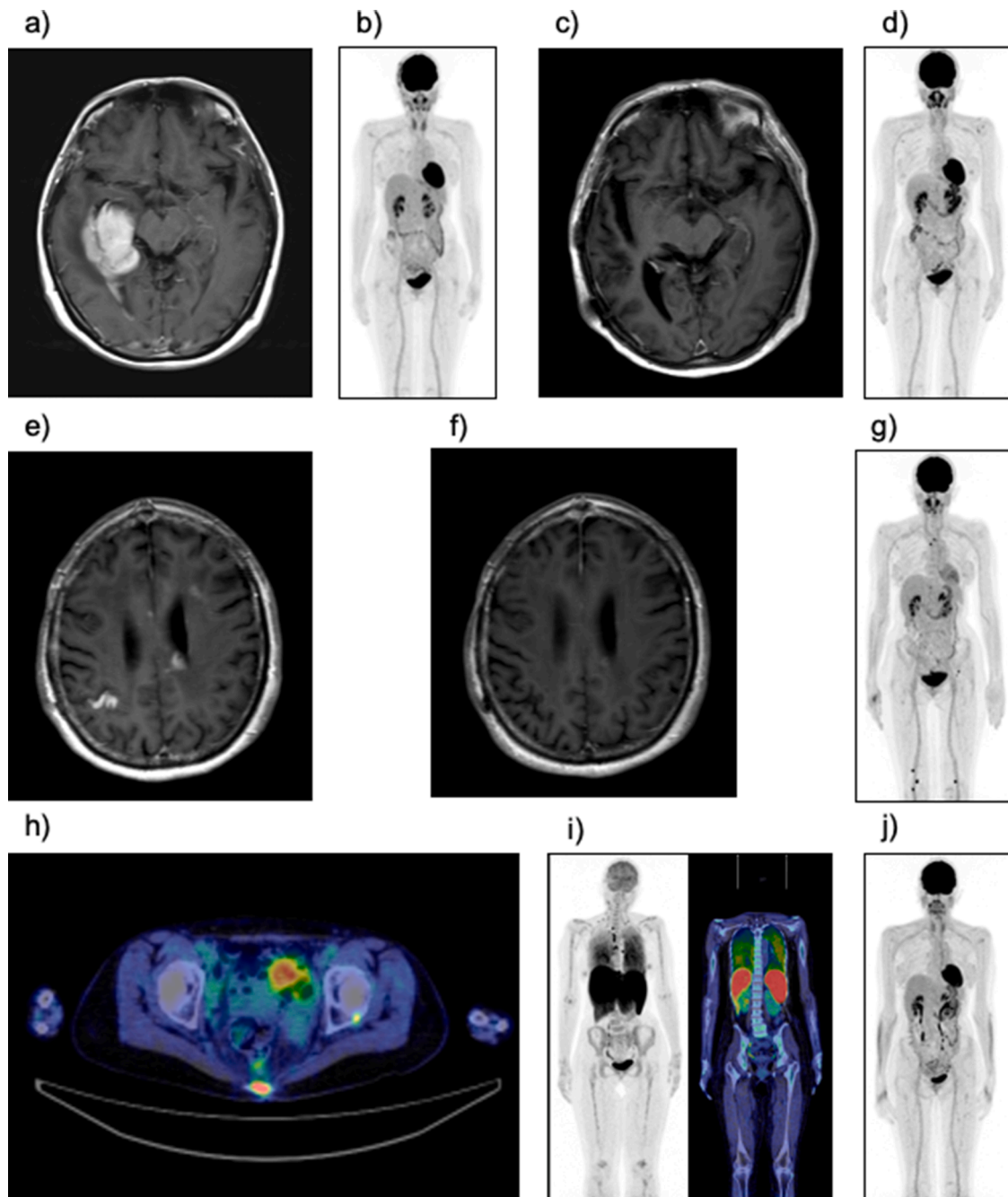
Eighteen months later, she was taken to the hospital for left arm weakness. Brain MRI showed new masses in the right temporal and frontal lobes (Fig. 1e). Since the lesions were symptomatic and not typical for PCNSL recurrence, second biopsy was performed. On immunohistochemical analysis, the tumor cells were positive for CD5,

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CD20, BCL2, and BCL6 and negative for CD3, CD10, MUM1, cyclinD1, and EBER. The Ki-67 labeling index was approximately 80%, and the c-myc protein was observed in approximately 40% of tumor cells. No other abnormal mass or bone marrow involvement was observed; this was confirmed using whole body CT and bone marrow biopsy, respectively, and led to the diagnosis of PCNSL recurrence. Four cycles of HD-MTX were administered again, and peripheral blood stem cells were harvested using plerixafor and granulocyte colony-stimulating factors.

After two additional cycles of HD-MTX therapy, there were no visible masses on MRI (Fig. 1f). However, PET-CT showed abnormal FDG uptake in several bone lesions, including the thoracic vertebrae, coccyx, and femur (Fig. 1g). Biopsy of the coccyx, which had the maximum standardized uptake value (SUV) (10.52) (Fig. 1h) among the lesions observed on PET-CT, was performed. This led to a suspicion of breast cancer metastasis. Because PCNSL was defined as complete remission, considering the prognosis of breast cancer and PCNSL, autologous



**Fig. 1.** Changes in brain magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT). **a** A mass lesion in the right temporal lobe was detected on brain MRI (T1-weighted) at the time of diagnosis of primary central nervous system lymphoma (PCNSL). **b** No abnormal uptake on PET-CT was detected at the time of diagnosis. After six cycles of high-dose methotrexate (HD-MTX) therapy, there were no visible masses on brain MRI (**c**) and no abnormal findings were observed on PET-CT (**d**). **e** Several masses were seen in the right temporal and frontal lobes on brain MRI (T1-weighted) at the time of recurrence. **f** After six cycles of HD-MTX therapy, there were no visible masses on MRI. **g** Abnormal  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) uptake in several bone lesions, including the thoracic vertebrae, coccyx, and femur, was detected on PET-CT. **h** The maximum standardized uptake value of the coccyx was 10.52, and biopsy of this lesion was performed. **i** Abnormal FDG uptake was observed in the liver (maximum standardized uptake value [SUV max] = 7.15), spleen (SUV max = 14.23), bilateral lung fields, and bone marrow at the time of diagnosis of intravascular large B-cell lymphoma. **j** After six cycles of DA-EPOCH-R (dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone and rituximab) therapy, PET-CT showed complete metabolic remission.

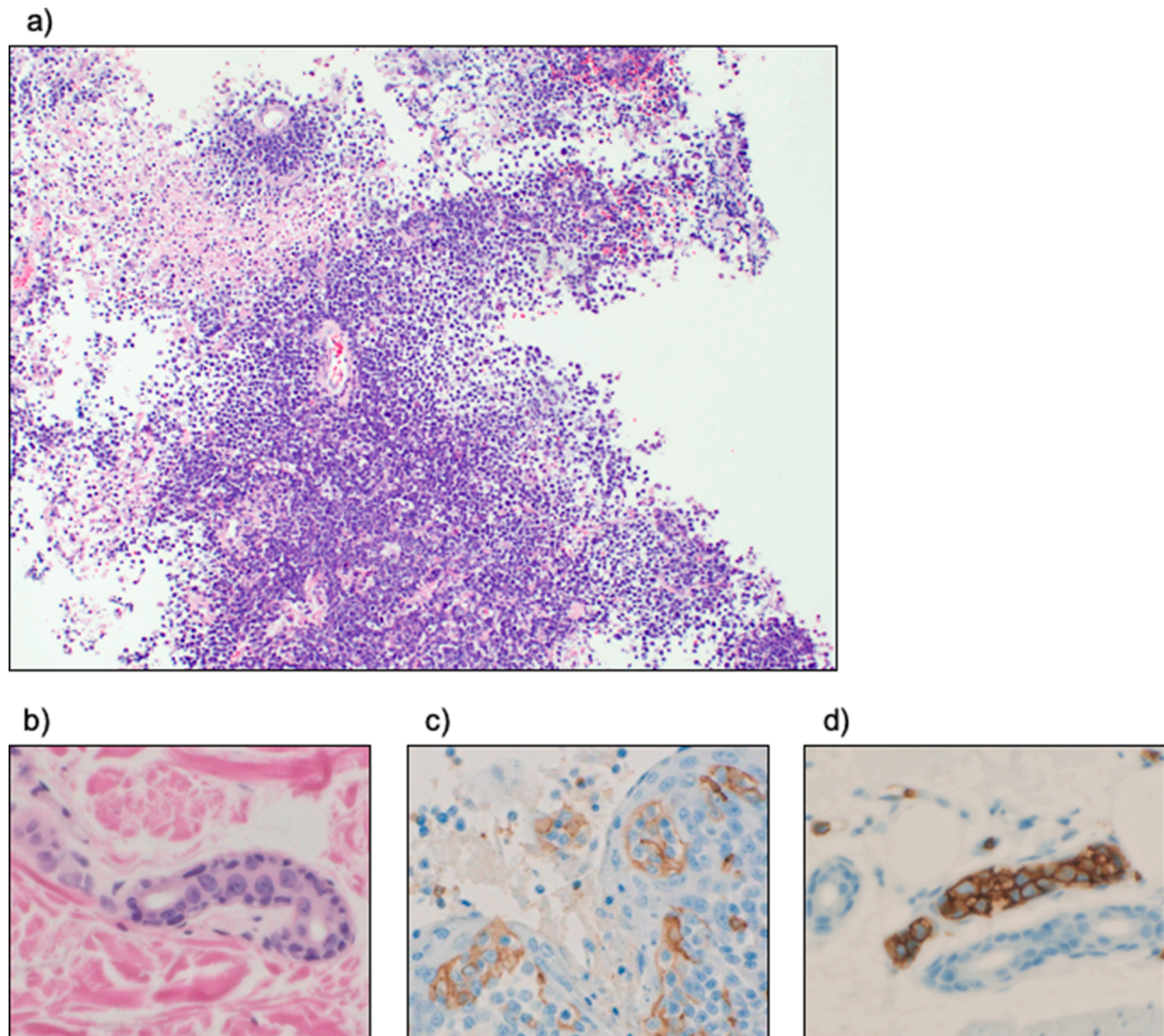
peripheral blood stem cell transplantation (auto-PBSCT) was performed using BU-CY-VP16 (busulfan, cyclophosphamide, and etoposide) as the conditioning regimen. No particular adverse events of special interest occurred, and the patient was discharged 19 days after auto-PBSCT.

Three weeks after her discharge from the hospital, she returned complaining of fever that started 1 week before her consultation. Her hematologic investigations showed elevated alkaline phosphatase (ALP) (3275 U/l) and C-reactive protein levels (17.4 mg/ml). PET-CT showed prominent hepatosplenomegaly with abnormal FDG uptake (Fig. 1i). Abnormal FDG uptake was also observed in the bilateral lung fields and bone marrow. However, the abnormal FDG uptake in the bone lesions, which was observed before auto-PBSCT and finally diagnosed as DLBCL by histological analysis, disappeared. Besides these findings, elevated soluble IL-2 receptor levels (7300 U/mL) suggested IVLBCL. A random skin biopsy was performed, and all biopsied specimens demonstrated obstruction of the small vessels by large lymphoid cells (Fig. 2b–d). On immunohistochemical examination, the tumor cells were positive for CD5, CD20, BCL2, and BCL6 and negative for CD10, cyclinD1, and EBER. The Ki-67 labeling index was approximately 90%, and the c-myc protein was observed in approximately 40% of tumor cells. Bone marrow biopsy also showed invasion by CD5-positive large B cells, and therefore, IVLBCL was diagnosed.

Administration of vincristine and prednisolone followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) improved her fever and ALP levels. However, since she had a history of chemotherapy for breast cancer (FEC therapy: fluorouracil, epirubicin, and cyclophosphamide), eight cycles of CHOP could not be administered owing to the possibility of anthracycline accumulation. Thus, we administered DA-EPOCH (dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) and rituximab (DA-EPOCH-R) therapies. After six cycles of DA-EPOCH-R therapy, PET-CT showed complete metabolic remission (Fig. 1j). The patient has been well for the last 6 months with no new symptoms.

### 3. Discussion

IVLBCL, a rare subtype of DLBCL, used to exhibit an extremely unfavorable progression. This unfavorable progression results from the difficulty to diagnose IVLBCL accurately given its heterogeneous symptoms and the absence of lymphadenopathies. It can involve several organs, such as the bone marrow, liver, spleen, skin, lungs, and adrenal glands, leading to various symptoms [3]. Additionally, before the rituximab era, the efficacy of chemotherapy was poor. Ferreri et al. reported a 3-year overall survival rate of 33% in 22 patients with IVLBCL



**Fig. 2.** a Pathological findings of the cerebrum reveals proliferative tumor cells diffusely infiltrating the central nervous system (hematoxylin and eosin staining). Pathological findings of random skin biopsy. b The lumens of the small blood vessels were occupied by large lymphoid cells (hematoxylin and eosin staining), which were positive for CD5 (c) and CD20 (d).



[4]. However, IVLBCL has become more recognized, and the rate of early diagnosis has increased. In addition, PET-CT might be useful in the diagnosis of IVLBCL, especially when there are no significant findings when using the conventional diagnostic methods [5,6]. Moreover, the use of rituximab as a chemotherapeutic agent has improved the prognosis. Shimada et al. showed that the 2-year overall survival of patients who received chemotherapy with and without rituximab were 66% and 46%, respectively [7].

The clinical and histopathological characteristics of IVLBCL in patients from Western countries differ from those of patients from Asian countries. The former show more central nervous system (CNS) and cutaneous symptoms, while the hemophagocytic syndrome occurs more in the latter. In our case, the patient showed bone marrow involvement, fever, hepatosplenomegaly, and thrombocytopenia, which are typical characteristics of an Asian variant [8], but no hemophagocytic syndrome. An elevated soluble IL-2 receptor level was also a valuable factor, which suggested the presence of IVLBCL and decreased to the normal level after chemotherapy.

Although the definition of IVLBCL includes the absence of malignant cells in lymph nodes, some patients with contamination of IVLBCL and other non-Hodgkin lymphomas (NHLs) have been reported. Moreover, IVLBCL can present as a recurrence of other DLBCLs, which are described in few reports. Kano et al. reported a case of relapse as IVLBCL after chemotherapy for CD5-positive DLBCL that primarily originated from the nasal cavity [9]. Zlotnick et al. presented the case of a patient diagnosed with IVLBCL who had been treated for testicular B-cell NHL 16 years earlier. They confirmed that the IVLBCL was a recurrence of testicular NHL by showing the identical size of the FR3 region of the *IgH* gene rearrangement from both specimens detected by polymerase chain reaction [10]. However, we could not find any previous reports of IVLBCL relapse after chemotherapy for PCNSL.

The high incidence of CNS progression during and after chemotherapy in IVLBCL has been reported. However, CNS involvement can be detected using CT and/or MRI in only half of the patients who present with CNS symptoms [3]. In contrast, IVLBCL sometimes presents with masses in the CNS, making it difficult to be differentiated from PCNSL [11]. Therefore, there is a possibility that IVLBCL in the CNS may be misdiagnosed as PCNSL. However, our patient had no clinical signs of IVLBCL at the time of initial diagnosis of PCNSL. There were neither detectable lesions on PET-CT nor B symptoms. Therefore, in this patient, the initial diagnosis was most probably PCNSL and not IVLBCL. However, the CNS and skin specimens were insufficient to analyze the *IgH* gene rearrangement; thus, we could not demonstrate that both diseases had the same origin. Nevertheless, the histopathological features of the PCNSL specimens and the random skin biopsy findings were nearly similar, suggesting that IVLBCL was the recurrence of PCNSL rather than a separate entity.

In conclusion, we report a case that was first diagnosed as PCNSL and that then relapsed as IVLBCL. To the best of our knowledge, this is the

first such case. Our case and the reported evidence showing high incidence of CNS invasion in IVLBCL suggest that the pathophysiology of PCNSL and IVLBCL may be related to each other.

## Declaration of Competing Interest

The authors declare no conflict of interest regarding this report.

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