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Case Report

Clinical utility of positron emission tomography leading to rapid and accurate diagnosis of intravascular large B-cell lymphoma presenting with the central nervous system symptoms alone: A case report and review of the literature

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ABSTRACT

Background: Intravascular large B-cell lymphoma (IVLBCL) is a rare entity among large B-cell non-Hodgkin lymphomas and is often difficult to diagnose. We report the case of a patient with IVLBCL who presented with central nervous system (CNS) symptoms alone, in which positron emission tomography (PET) enabled a rapid and accurate diagnosis.

Case Description: An 81-year-old woman was admitted to our hospital with a 3-month history of gradually progressive dementia and declining spontaneity. Magnetic resonance imaging revealed multiple hyperintense lesions bilaterally on diffusion-weighted imaging without enhancement on gadolinium-enhanced T1-weighted imaging. Laboratory findings showed elevated serum lactate dehydrogenase (626 U/L) and soluble interleukin-2 receptor (sIL-2R) (4692 U/mL). Cerebrospinal fluid (CSF) analysis showed slightly elevated levels of protein (166 mg/dL) and lymphocytic cells (29/μL), and β2-microglobulin (β2-MG) (4.6 mg/L) was highly elevated. Whole-body computed tomography revealed faint ground-glass opacities in the upper and middle lung fields and diffuse enlargement of both kidneys without lymph node swelling. ^{18}F-fluorodeoxyglucose (FDG)-PET showed diffuse and remarkably high FDG uptake in both upper lungs and kidneys without uptake by lymph nodes, suggesting a malignant hematological disease. IVLBCL was confirmed histologically by incisional random skin biopsy from the abdomen. Chemotherapy using R-CHOP regimen in combination with intrathecal methotrexate injection was started on day 5 after admission and follow-up neuroimaging showed no signs of recurrence.

Conclusion: IVLBCL presenting with CNS symptoms alone is rare and often has a poor prognosis associated with delayed diagnosis, and various evaluations (including systemic analysis) are therefore necessary for early diagnosis. FDG-PET, in addition to identification of clinical symptoms and evaluation of serum sIL-2R and CSF β2-MG, enables rapid therapeutic intervention in IVLBCL presenting with CNS symptoms.

Keywords: ^{18}F-fluorodeoxyglucose, Intravascular large B-cell lymphoma, Positron emission tomography, Random skin biopsy, R-CHOP

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare entity of large B-cell non-Hodgkin lymphoma that is characterized by selective proliferation of large cells within the lumen of small- and medium-sized vessels of various organs.[10,14] IVLBCL displays a relatively high frequency of central nervous system (CNS), skin, and bone marrow involvement.[11,14] Neurological symptoms are highly heterogeneous, including dementia, hemiparesis, seizures, myoclonus, and mental changes.[7,14] This disease is more common in middle-aged and elderly patients. As the rapid progression of symptoms can lead to a poor prognosis, accurate diagnosis followed by early treatment is essential. Histological evidence of the presence of tumor cells is required for a definitive diagnosis, and the bone marrow and skin are often selected as biopsy sites as they are less invasive than the alternatives. In some patients, however, it can be difficult to obtain a diagnosis based on such biopsies. If the possibility of this disease is suspected, it is therefore important to perform targeted biopsy. Here, we report that the case of a patient who presented with progressive dementia and was diagnosed with IVLBCL based on random skin biopsy. The ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) findings were useful in obtaining a rapid and accurate diagnosis that enabled early therapeutic intervention.

CASE DESCRIPTION

An 81-year-old woman presented to our department with a 3-month history of gradually progressive dementia and decline in spontaneity. She had no medical history of atrial fibrillation. Neurological examination on admission revealed disturbance of consciousness but no weakness of the extremities. Her score of 12/30 on the mini-mental state examination (MMSE) indicated severe cognitive impairment. No fever or skin eruptions were present. Neuroimaging on magnetic resonance imaging demonstrated multiple hyperintense lesions bilaterally, including in the periventricular white matter, centrum semiovale, and corpus callosum on diffusion-weighted imaging and fluid attenuated inversion recovery. The lesions showed no enhancement on T1-weighted imaging following administration of gadolinium [Figure 1]. Electroencephalography (EEG) revealed epileptic discharge mainly in the right frontal lobe. Laboratory findings showed elevated serum lactate dehydrogenase (LDH) (626 U/L), C-reactive protein (CRP)

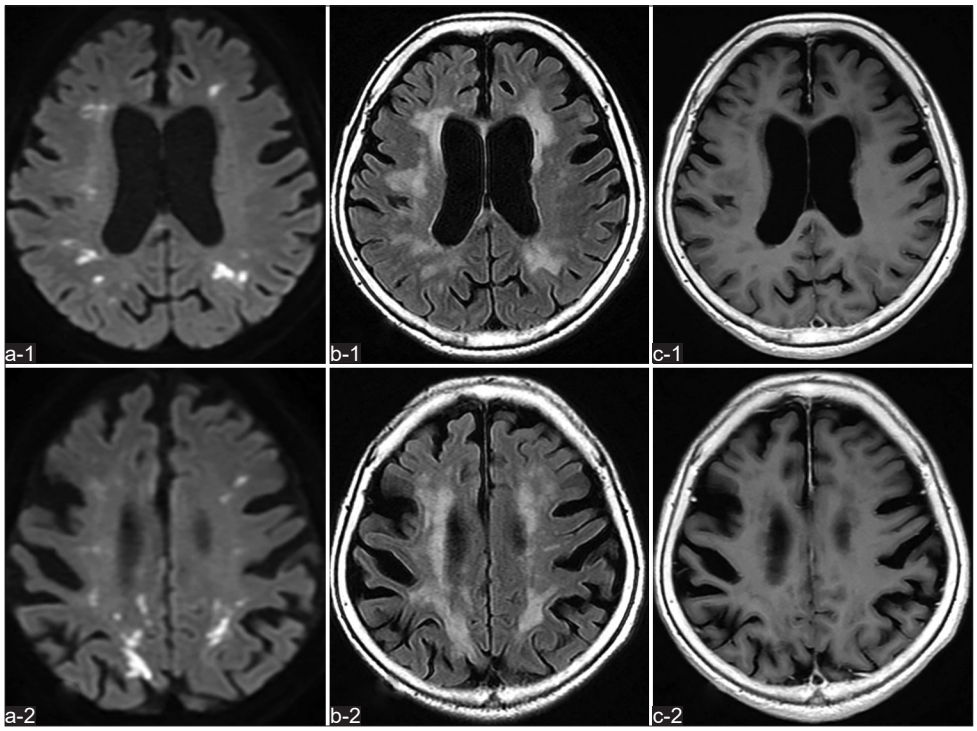

Figure 1: Magnetic resonance imaging findings of the brain. Axial diffusion-weighted imaging (a-1 - a-2) and fluid-attenuated inversion recovery imaging (b-1 - b-2) obtained at admission reveal multiple hyperintense lesions bilaterally in the periventricular white matter, centrum semiovale, and corpus callosum. T1-weighted imaging (c-1 - c-2) acquired after injection of gadolinium contrast medium shows no enhancement of the lesions.

(13.31 mg/dL), and soluble interleukin (IL)-2 receptor (sIL-2R) (4692 U/mL). Cerebrospinal fluid (CSF) analysis revealed slightly elevated levels of protein (166 mg/dL) and lymphocytic cells (29/μL), and highly elevated β2-microglobulin (β2-MG) (4.6 mg/L). Whole-body computed tomography revealed faint ground-glass opacities in the upper and middle lung fields and diffuse enlargement of the bilateral kidneys without lymph node swelling. FDG-PET showed no obvious FDG accumulation in the brain. There was diffuse FDG uptake in both the upper and middle lungs without uptake by lymph nodes and remarkably high FDG uptake in the bilateral kidneys, suggesting a malignant hematological disease [Figure 2]. Bone marrow biopsy and incisional random skin biopsy from the abdomen were performed. The bone marrow puncture contained no neoplastic cells, but the pathologic specimen obtained by skin biopsy showed occlusion of small vessels by neoplastic cells with prominent nucleoli inside the subcutaneous adipose tissue [Figures 3a and b]. Immunohistochemical examination revealed cluster of differentiation (CD) 79a (+), CD20 (+) and CD3 (−), suggesting multiorgan infiltration of B lymphohematopoietic system tumors [Figures 3c and d]. In addition, non-germinal center B-cell like phenotype was identified from the results of CD10 (+), bcl-6 (+), and MUM1 (+) according to the decision tree proposed by Hans *et al*.[4] The patient was negative for Epstein Barr virus (EBV) and the result of *in situ* hybridization using EBV-encoded small nuclear early region was negative, indicating that EBV infection was not related to IVLBCL in this case. At day 5 after admission to our institution, the patient began treatment with complete cyclophosphamide, doxorubicin, vincristine, and prednisolone with rituximab (R-CHOP) in combination with intrathecal methotrexate injection. At 1 month after admission, follow-up neuroimaging showed no signs of recurrence [Figure 4], no epileptic discharges were seen on EEG, and her MMSE score had improved to 27/30. After three cycles of R-CHOP in combination with intrathecal methotrexate injection, the patient's serum LDH, CRP, and LDH, and CSF β2-MG levels normalized; and there was complete disappearance of the FDG accumulation in the lung and kidney on FDG-PET [Figure 5], and the patient achieved complete metabolic remission.

DISCUSSION

IVLBCL is a rare and fatal subtype of extranodal B cell lymphoma characterized by the selective growth of lymphoma cells, particularly in capillaries, in multiple

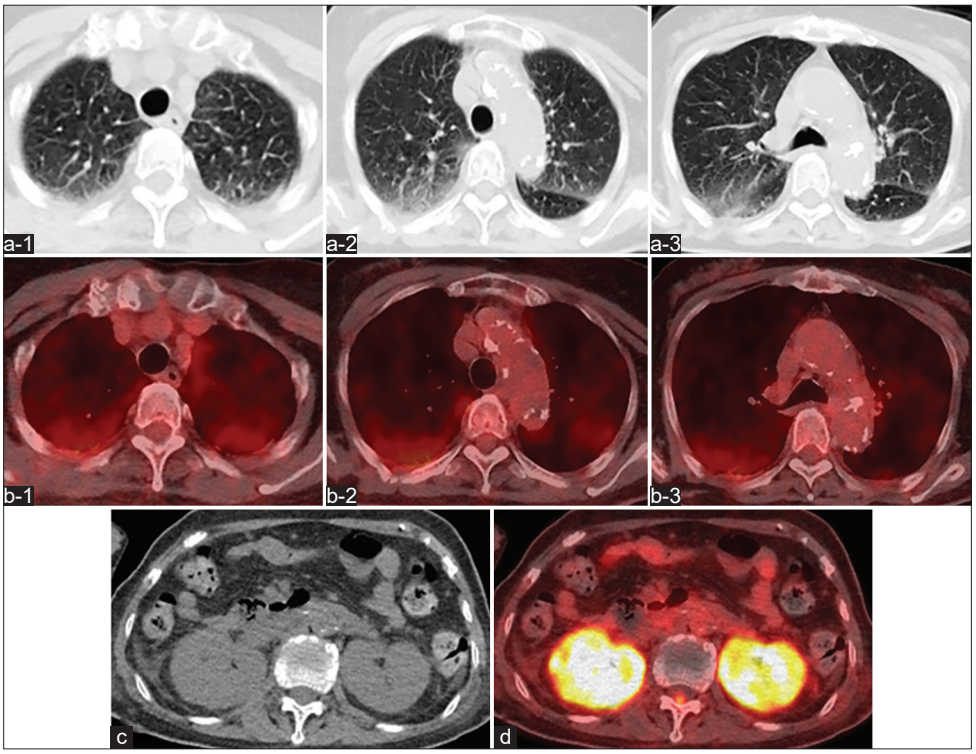

Figure 2: Axial computed tomography (CT) of the chest (a-1 - a-3) shows faint diffuse ground glass opacities in the upper and middle lung fields bilaterally. 18 F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) (b-1 - b-3) reveals slightly diffuse FDG uptake in the upper and middle lung fields bilaterally without uptake by lymph nodes. CT of the abdomen (c) demonstrates diffuse enlargement of both kidneys without lymph node swelling. FDG-PET (d) shows remarkably high FDG uptake in both kidneys.

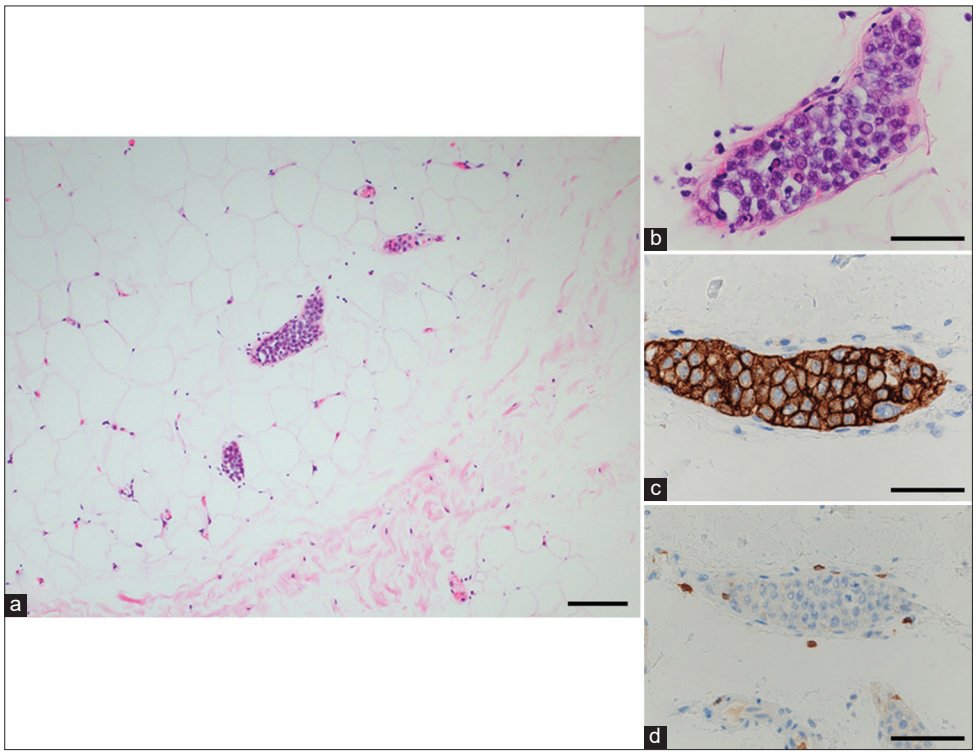

Figure 3: Histopathology of the resected lesion by random skin biopsy. Pathologic specimen (a and b) shows occlusion of small vessels by neoplastic cells with prominent nucleoli within subcutaneous adipose tissue. Tumor cells show positive staining for CD20 (c) and negative staining for CD3 (d). Magnification: (a) ×200; (b-d) ×400. Scale bars, 100 μm.

organs.[7,10,11,13,14] The proliferation of lymphoma cells within vessels causes clinical symptoms according to the organs affected and can include neurologic, hematologic, skin, bone marrow, and pulmonary involvement.[15] The incidence of this lymphoma is less than 1.0 per million. The median age of patients is 70.0 years, with the same frequency between males and females.[8] In general, the clinical presentation of IVLBCL is highly variable, making it difficult to diagnose. Two main variants have been reported in cases from Western countries, manifesting with relatively high frequencies of either skin rashes or multiple neurological deficits.[6,14] However, IVLBCL often presents with a set of non-specific clinical characteristics resulting from involvement of one or several organs.[14] Fever, general malaise, neurological symptoms, and dyspnea are frequently observed as symptoms associated with IVLBCL. The incidence of CNS involvement throughout the course of IVLBCL is high, ranging from 70% to 85%.[1] Glass *et al*. reported that progressive and multifocal cerebrovascular disease occurs in 76% of patients, spinal cord and nerve root damage in 38%, subacute encephalopathy in 27%, cerebral neuropathy in 21%, and peripheral neuropathy in 5.0%.[3] The present case also had unexplained epileptic seizures, which may be an important finding indicating the possibility of IVLBCL.

Suspicion of IVLBCL is a crucial first step in the treatment process because IVLBCL has a poor prognosis when therapeutic intervention is delayed. The prognosis of IVLBCL patients will be greatly improved when they obtain a timely and accurate diagnosis and appropriate treatment. Accordingly, further investigations should be performed particularly in the presence of unexplained fever, skin rash, or neurologic manifestations. The laboratory findings of high serum LDH, CRP, and sIL2-R levels, anemia, and thrombocytopenia due to tumor infiltration of the bone marrow and hemophagocytosis are common in IVLBCL. Regarding CSF analysis, a previous study has reported that C-X-C motif chemokine ligand 13, IL-10, sIL-2R, and β2-MG have excellent diagnostic ability for primary CNS lymphoma.[5] In the present patient, serum LDH, CRP, and sIL2-R were elevated and CSF analysis revealed extremely high β2-MG. FDG-PET is also valuable for the diagnosis of IVLBCL due to its sensitivity in organs with a rich blood supply, specifically the lungs and kidneys.[9] Tobin-Vealey *et al*. analyzed three cases of IVLBCL and reported that FDG-PET could help support a diagnosis of IVLBCL when clinical suspicion was high. The imaging findings can also be useful for identifying an appropriate site for biopsy to

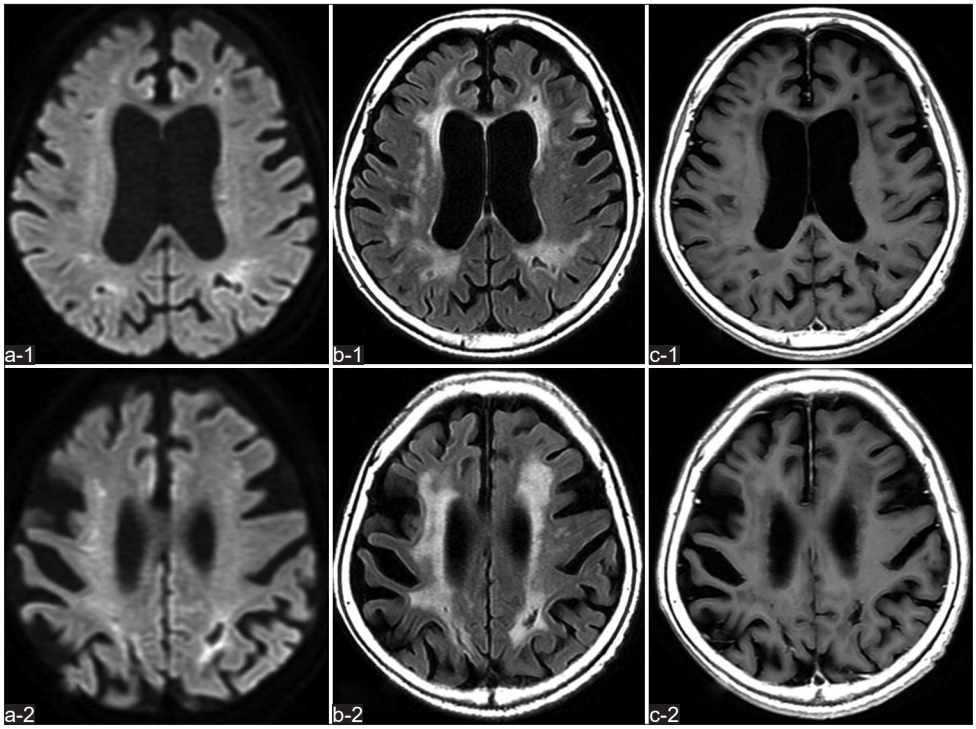

Figure 4: Brain magnetic resonance imaging (MRI) findings at 1 month after admission. The multiple high-intensity lesions apparent on MRI obtained at admission have decreased on diffusion-weighted imaging (a-1 - a-2), and no new lesions are identified on fluid-attenuated inversion recovery imaging (b-1 - b-2) and gadolinium-enhanced T1-weighted imaging (c-1 - c-2).

confirm diagnosis.[12] Although there was no obvious FDG accumulation in the brain in the present case, FDG-PET showed diffuse and remarkably high FDG uptake in both upper lungs without uptake by lymph nodes and there was remarkably high uptake in both kidneys, suggesting a malignant hematological disease. This finding may be extremely useful in the early diagnosis of IVLBCL and in determining an appropriate biopsy site.

When IVLBCL is suspected based on the aforementioned symptoms and laboratory findings, pathological confirmation of tumor cells is the gold standard for diagnosis.[7,10,11,13,14] Identification of large tumor cells within the small vessels or sinusoids of an organ on an appropriate biopsy image is diagnostic for IVLBCL.[7,10,11,13,14] The combination of random skin biopsy and bone marrow puncture/biopsy has become commonly performed since the 2000s and enabled diagnosis in many cases. This method is less invasive than biopsies of deeper organs and has diagnostic value even when the symptoms and abnormalities are mild. When IVLBCL is suspected, it is recommended that this combination should be performed as a priority. Enzan *et al*. reported that of 82 random skin biopsies from 25 patients with IVLBCL, 46% had tumor cells only in subcutaneous adipose tissue and the median minimum depth from the skin surface where tumor cells were found was 3.64 mm. In 37% of cases, tumor cells were larger than 5 mm. Incisional biopsies should be performed keeping in mind that tumor cells are found only in the vessels of subcutaneous adipose tissue.[2] In the present case, bone marrow biopsy did not lead to a diagnosis but random skin biopsy confirmed the presence of CD 20 (+) tumor cells in the microvasculature of subcutaneous fat tissue, thus providing a rapid and minimally invasive diagnosis of IVLBCL.

There are several important observations and findings in the present case. First, IVLBCL should be considered in patients who present with rapid progressive dementia and cerebral infarction with elevated serum LDH, CRP and sIL2-R, and CSF β2-MG. Second, because IVLBCL is a systemic disease, FDG-PET may be very useful for obtaining an early and accurate diagnosis, even if only neurologic symptoms are present. Third, because appropriate treatment can improve outcomes, a timely and accurate diagnosis is crucial for patients with IVLBCL. Therefore, early random skin biopsy should be considered if IVLBCL is suspected. Further experience with this therapy and longer patient follow-up is required.

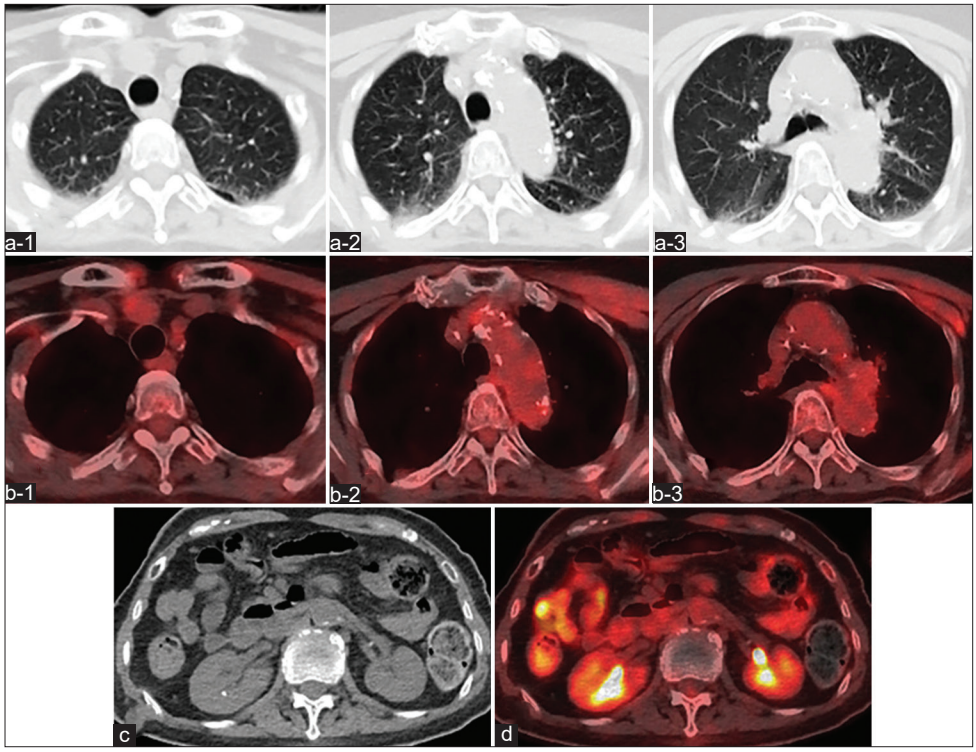

Figure 5: Whole body computed tomography (a-1 - a-3 and c) and ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (b-1 - b-3 and d) obtained after three cycles of chemotherapy show complete disappearance of the abnormal signs and FDG accumulation identified on admission, indicating achievement of complete remission.

CONCLUSION

As IVLBCL is a very rare entity and often has a poor prognosis, it is necessary to quickly identify the possibility of IVLBCL based on the laboratory findings followed by appropriate biopsy to enable early therapeutic intervention. In the present patient, FDG-PET supported the diagnosis of IVLBCL when clinical suspicion was high. In aged patients with progressive cerebral infarction as well as cognitive decline and recurrent epileptic seizures, it may be important to perform whole-body FDG-PET in addition to analysis of serum sIL-2R and CSF β2-MG, considering the possibility of IVLBCL.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Chapin JE, Davis LE, Kornfeld M, Mandler RN. Neurologic manifestations of intravascular lymphomatosis. Acta Neurol Scand 1995;91:494-9.
2. Enzan N, Kitadate A, Tanaka A, Matsue K. Incisional random skin biopsy, not punch biopsy, is an appropriate method for diagnosis of intravascular large B-cell lymphoma: A clinicopathological study of 25 patients. Br J Dermatol 2019;181:200-1.
3. Glass J, Hochberg FH, Miller DC. Intravascular lymphomatosis. A systemic disease with neurologic manifestations. Cancer 1993;71:3156-64.
4. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, *et al*. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-82.
5. Maeyama M, Sasayama T, Tanaka K, Nakamizo S, Tanaka H, Nishihara M, *et al*. Multi-marker algorithms based on CXCL13, IL-10, sIL-2 receptor, and β2-microglobulin in cerebrospinal fluid to diagnose CNS lymphoma. Cancer Med 2020;9:4114-25.
6. Ponzoni M, Ferreri AJ, Campo E, Facchetti F, Mazzucchelli L, Yoshino T, *et al*. Definition, diagnosis, and management of intravascular large B-cell lymphoma: Proposals and perspectives from an international consensus meeting. J Clin

Oncol 2007;25:3168-73.
7. Ponzoni M, Campo E, Nakamura S. Intravascular large B-cell lymphoma: A chameleon with multiple faces and many masks. Blood 2018;132:1561-7.
8. Porzionato A, Pelletti G, Barzon L, Contran M, Emmi A, Arminio A, *et al*. Intravascular large B-cell lymphoma affecting multiple cranial nerves: A histopathological study. Neuropathology 2021;41:396-405.
9. Shiiba M, Izutsu K, Ishihara M. Early detection of intravascular large B-cell lymphoma by (18) FDG-PET/CT with diffuse FDG uptake in the lung without respiratory symptoms or chest CT abnormalities. Asia Ocean J Nucl Med Biol 2014;2:65-8.
10. Shimada K, Kinoshita T, Naoe T, Nakamura S. Presentation and management of intravascular large B-cell lymphoma. Lancet Oncol 2009;10:895-902.
11. Tahsili-Fahadan P, Rashidi A, Cimino PJ, Bucelli RC, Keyrouz SG. Neurologic manifestations of intravascular large B-cell lymphoma. Neurol Clin Pract 2016;6:55-60.
12. Tobin-Vealey K, Jain S, Al Diffalha S, Sohn A, Henry E, Czerlanis C, *et al*. Use of fluorodeoxyglucose-positron emission tomography in the diagnosis of intravascular diffuse large B-cell lymphoma. Fed Pract 2016;33:32S-6.
13. Tsuji M, Kondo M, Onizawa F, Shishime O, Muramatsu S, Matsuo Y, *et al*. A case of lung intravascular large B cell lymphoma developed with respiratory failure rescued by corticosteroid prior to definite diagnosis. Respir Med Case Rep 2022;37:101625.
14. Wu M, Lin Y, Huang X, Zhang B. Intravascular large B-cell lymphoma presenting as rapidly progressive dementia and stroke: A case report. Medicine (Baltimore) 2021;100:e27996.
15. Zhu D, Shen Y, Huang J, Zhao L. Intravascular large B-cell lymphoma with diffuse ground glass lesion on chest computed tomography diagnosed using transbronchial lung cryobiopsy: A case report. Transl Cancer Res 2021;10:4571-6.

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