CASE REPORT

Nagoya J. Med. Sci. **74**. 353 ~ 358, 2012

INTRAVASCULAR LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM PRESENTING AS MULTIPLE CEREBRAL INFARCTIONS

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ABSTRACT

A 67-year-old woman presented with an acute onset of left-sided weakness. Magnetic resonance (MR) imaging revealed multiple cerebral infarctions and gadolinium-enhanced lesions in both cerebral hemispheres. Her symptoms once improved after starting steroid treatment; however, soon developed consciousness disturbance and hemiparesis on the left side. She was referred to our hospital where she underwent stereotactic needle biopsy, that revealed an intravascular large B-cell lymphoma in the cerebrum. She received high-dose methotrexate chemotherapy followed by whole-brain radiation therapy, and the MR findings improved. However, her medical condition gradually worsened, and she died 6 months after disease onset. Intravascular lymphoma (IVL) limited to the central nervous system (CNS) is very rare, and the optimal treatment for this medical condition has not been established yet. IVLs showing only neurologic manifestations might be overlooked or misdiagnosed as cerebral infarctions. Here, we present a case of CNS IVL, with its radiographic and pathologic features and treatment with high-dose methotrexate chemotherapy.

Key Words: Intravascular lymphoma, Central nervous system, Cerebral infarction

INTRODUCTION

Intravascular lymphoma (IVL) is a rare variant of mature B-cell neoplasms restricted to the vascular lumina, and this condition preferentially affects the central nervous system (CNS) and skin. One-third of IVL patients presents with heterogeneous neurological symptoms at diagnosis.[1)] In cases of CNS involvement, most of the common symptoms observed are related to ischemia and infarction due to small vessel occlusion by the tumor cells. However, IVL limited to the CNS is an extremely rare condition as IVL is usually found with systemic lesions. Only a few such cases have been reported thus far.[2)] Regional differences of IVL are also known; for example, CNS and cutaneous involvement are less common in the Asian variant than in the Western variant.[1,3)] Under these conditions, isolated IVL of the CNS tends to be overlooked or

Received: July 13, 2012; accepted: July 19, 2012

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misdiagnosed as cerebral infarctions, especially in Asian countries. The optimal treatment of CNS IVL has not been established yet, and only a few reports are available on the treatment with high-dose methotrexate-based chemotherapy in the literature.[4,5] Here, we report the case of an IVL patient with similar neurologic and radiographic findings of cerebral infarctions at the onset of disease, who received high-dose methotrexate chemotherapy and radiotherapy.

CASE REPORT

A 67-year-old Japanese woman, without previous medical history, developed left-sided weakness and was admitted to the hospital. Brain magnetic resonance (MR) images showed multiple ischemic lesions, and she was treated for cerebral infarctions, despite the coexistence of gadolinium-enhanced lesions (Figs. 1A and 1B). Her symptoms once improved after steroid administration (betamethasone 4–8 mg/body); however, she developed consciousness disturbance and hemiparesis on the left side. Five weeks after disease onset, she was transferred to our hospital. On the second admission, laboratory examination of her blood revealed high levels of serum lactate dehydrogenase (LDH; 256 U/L) and soluble interleukin-2 receptor (sIL-2R; 5,896 U/mL). Her electronic cardiogram indicated either acute myocardial infarction or cardiomyopathy, wherease serum troponin T was negative. Bone marrow aspiration and fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) did not show any evidence of systemic malignancy. Cerebrospinal fluid cytology was performed, and no malignant cells were observed. A repeat MR imaging performed 6 days after the second admission showed progressive ischemic lesions detected by fluid-attenuated inversion recovery imaging (Fig. 1C), whereas MR angiography did not show any abnormality in the major cerebral arteries. Because the MR imaging results and the patient's history of the present illness indicated a neoplastic disease, stereotactic needle biopsy of her right frontal lobe (enhanced lesion in Fig. 1B) was performed on day 7 after admission. Hematoxylin and eosin staining of the specimen revealed intravascular accumulation of tumor cells (Fig. 2A). Immunostaining for the endothelial cell marker CD31 and the pan-B-cell marker CD20 showed neoplastic B-cells exclusively located in the blood vessel lumina (Figs. 2B and 2C). A pathological diagnosis of intravascular large B-cell lymphoma was concluded. Further immunohistochemical analysis was performed, and revealed that the tumor was negative for CD5, CD10, and BCL-6, and positive for MUM-1, indicating the post-germinal center B-cell subtype. She received 3 cycles of high-dose methotrexate (3.5 g/m^2) chemotherapy followed by whole-brain radiation therapy (30 Gy in 10 fractions). Although the gadolinium enhancement on MR images decreased, her general condition worsened and she died without regaining consciousness 6 months after disease onset. A postmortem pathological examination was not performed.

DISCUSSION

In the present case, the initial manifestation of neurologic signs and the ischemic findings on brain MR imaging made differential diagnosis difficult. Domizio et al. reported the 79 cases of IVL in 1989 and found that 32% of the patients had symptoms attributable to CNS lesions alone, whereas 12% had CNS and systemic symptoms.[6] This frequency of CNS symptoms alone seems high. However, as IVL is a systemic disease and owing to advances in imaging technology in the past 2 decades, asymptomatic lesions of other organs have been found in most cases. In fact, Ferreri et al. reported in 2004 that CNS lesions were detected in 40% of European IVL patients as multiorgan infiltration but lesions limited to the CNS were found only

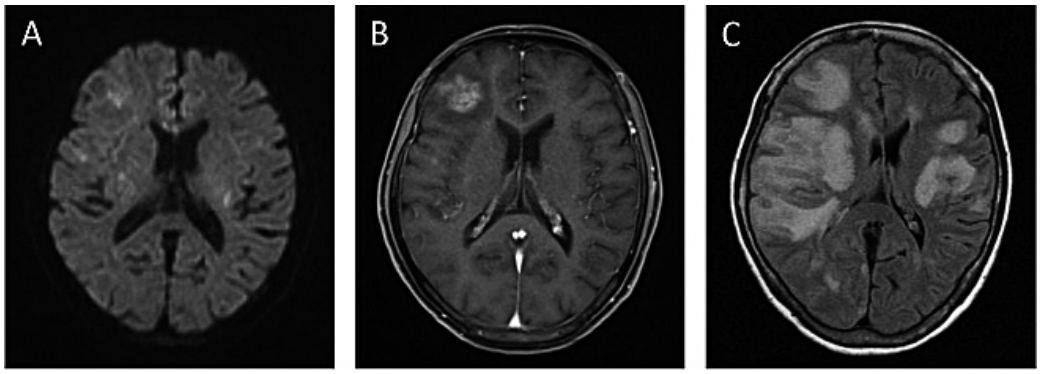

Fig. 1 (A) Diffusion weighted magnetic resonance (MR) image at disease onset showing multiple high intensity lesions in both cerebral hemispheres. (B) Gadolinium-enhanced T1 weighted MR image at disease onset showing the lesions with contrast enhancement mainly in the right frontal lobe. (C) Fluid-attenuated inversion recovery MR image performed 6 weeks after onset demonstrating multiple high intensity areas progressing in both cerebral hemispheres.

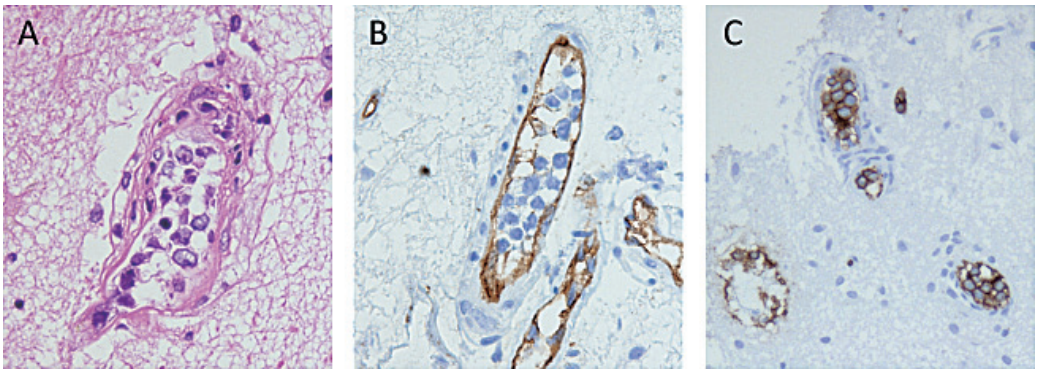

Fig. 2 (A) Hematoxylin and eosin staining showing intravascular accumulation of the neoplastic lymphoid cells. (B) CD31 staining demonstrating surrounding vascular endothelial cells. (C) Tumor embolisms consisting of CD20-expressing B-cells. Original magnifications, A and B: ×400, C: ×200.

in 5%.[7] An Asian retrospective study of 96 patients with IVL reported that CNS involvement accounted for 27%, and 2 of 81 (2.5%) IVL patients underwent brain biopsy, providing another evidence of this rare condition with restricted CNS involvement.[8] Heart involvement is also relatively rare. Reports from Western countries have described heart involvement in 11% of the cases, and cardiac dysfunction, as a presenting symptom, in 5% of the cases.[1,7] In our case, electronic cardiogram indicated the possibility of acute myocardial infarction, suggesting small vessel occlusion by tumor cells in the heart. However, serum cardiac troponin T, a diagnostic marker for myocardial infarction, was negative, and bone marrow aspiration and FDG-PET did not detect any systemic lesions.

Radiologic findings are nonspecific in IVL. In the present case, the initial findings of MR imaging was similar to multiple cerebral infarctions, while other rare CNS diseases such as mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) should be considered in the differential diagnosis. Cranial computed tomography (CT) scanning has been

reported to reveal multifocal hypodense lesions in up to 86% of histologically confirmed IVL cases.[9] However, CT is generally considered nondiagnostic in the early stage of IVL in the CNS because of possible false-negative results.[10] Hyperintense white matter lesions on T2-weighted MR images are suggestive of small-vessel ischemic condition in CNS IVL. On the other hand, others reported that neuroimaging, including MR imaging, did not detect brain lesions in half of the patients with neurological symptoms and an in vivo diagnosis of IVL.[7] Although T2-weighted MR images may be normal, cranial contrast-enhanced T1-weighted MR images have been reported to increase the sensitivity for detecting IVL involving the CNS.[10,11] Therefore, MR imaging of the CNS has been recommended to be routinely included in the diagnosis and staging of IVL.[7]

Serum and immunohistochemical markers of IVL have been tested, and the results have been reported from several groups. High serum LDH level (higher than the upper limit of the standard range) and sIL-2R level (5×10^3 U/mL or higher) were observed in 93% and 56% of Asian patients with IVL, respectively.[8] Immunopositivity for CD5, CD10, BCL-6, and MUM-1 were reported in 38%, 13%, 26%, and 95% of Asian IVL patients in the same series, respectively.[8] However, none of these serum and immunohistochemical markers had a significant effect on prognosis in IVL. These results of high CD5 and low BCL-6 positivity rates seem to differ from the rates reported in systemic or primary CNS diffuse large B-cell lymphomas.[12-16] The positivity rates and prognostic values of the immunohistochemical markers in IVL limited to the CNS remains to be elucidated because of the rarity of this disease.

The treatment for CNS IVL has not been established yet. Anthracycline-based chemotherapy has been reported to improve clinical outcomes for systemic IVL patients[17] and has been considered a standard treatment for IVL with a 3-year overall survival rate of 33%.[18] More recently, the effect of rituximab-containing chemotherapy has been indicated in a study of 106 patients with systemic IVL.[19] In contrast, the standard treatment for primary CNS lymphoma is methotrexate-based chemotherapy alone or in combination with whole-brain radiotherapy,[20] and it remains unclear whether IVL should be treated as primary CNS lymphoma when limited to the CNS. The intravascular growth pattern has been hypothesized to be secondary to defects in homing receptors present on the neoplastic cells, such as the lack of b1 integrin and intercellular adhesion molecule-1 (ICAM-1).[21,22] However, IVL seems to have the potential to lead to the development of an extravascular mass in the CNS.[23] Therefore, high-dose methotrexate therapy can be a treatment option for IVL limited to the CNS.

In conclusion, IVL with restricted CNS involvement is a rare condition, the treatment for which has not been thoroughly discussed in the literature. We here showed a case of IVL presenting with cerebral infarctions. While the symptoms and neuroimaging findings were confounding, the gadolinium enhancement on MR imaging was a clue to the diagnosis of IVL in this case. High-dose methotrexate therapy seemed to be a treatment option for CNS-limited IVL. Careful differential diagnosis is required when multiple acute cerebral infarctions with gadolinium enhancement are observed on MR imaging.

ACKNOWLEDGEMENT

We thank Dr. Akiko M Maeshima (Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan) for her pathology expertise.

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