A Case of Intravascular Lymphoma with Increased Regional Cerebral Blood Flow in I-123 IMP Single-Photon Emission CT

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Case Report

A Case of Intravascular Lymphoma with Increased Regional Cerebral Blood Flow in I-123 IMP Single-Photon Emission CT

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Summary: This report documents a case of intravascular lymphoma (IVL) with increased regional cerebral blood flow (rCBF) disclosed at I-123 IMP single-photon emission CT (IMP-SPECT). A 73-year-old woman with IVL had high rCBF disclosed by IMP-SPECT before chemotherapy; rCBF was normal after one course of CHOP (cyclophophamide, vincristine, doxorubicin, and prednisone) chemotherapy. During her clinical course, she had an episode in which she showed increased rCBF in the left cerebral hemisphere at IMP-SPECT performed immediately after the recovery from the right hemiparesis.

Intravascular lymphoma (IVL) is a rare, generally fatal, disease characterized by multifocal proliferation of lymphoma cells within the lumen of small vessels throughout the body. CNS involvement usually presents as subacute encephalopathy, dementia, seizure, or multifocal cerebrovascular events. Recently, CT and MR findings of the brain as multiple patchy white matter lesions or infarct-like lesions in IVL have been reported. By contrast, it has been known that IVL clinically mimics primary angiitis of CNS, and cerebral angiography reveals findings consistent with those of CNS vasculitis. This case may support that CNS manifestations of early-stage IVL mimic CNS vasculitis or encephalitis.

Case Report

A 73-year-old woman who was suspected of having malignant lymphoma after several weeks' history of general fatigue, anorexia, high fever, pancytopenia, high levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP), and phagocytosis in the bone marrow was admitted to our hospital in late November 1999. Laboratory findings on admission showed the following values: erythrocyte sedimentation rate, 62 mm/h; leukocytes, 5000/μL; erythrocytes, 266 $\times$ 10^4/μL; hemoglobin, 8.9 g/dL; hematocrit, 25.3%; platelets, 3.9 $\times$ 10^4/μL; CRP, 9.45 mg/dL; LDH, 3359 IU/L; soluble interleukin-2 receptor (sIL-2R), 13044u/mL. Bone marrow biopsy revealed diffuse large cell lymphoma that was positive for the leukocyte common antigen (LCA), and the B-cell marker. CSF protein level was 48 mg/dL. The cell number of CSF was 19/3, and cytology was class III of lymphocytes with enlarged nuclei. On the basis of clinical data and symptoms, intravascular lymphoma was diagnosed.

Brain MR imaging findings (Fig 1) showed minimal high intensity in the basal ganglia (BG) and thalamus (Th) on T2-weighted images, which may suggest minimal lacunar infarcts. A contrast-enhanced T1-weighted coronal image showed dural-arachnoid enhancement. On contrast-enhanced T1-weighted images, the bone marrow of the skull showed signal intensity prolongation, which implies bone marrow invasion or changes to red marrow due to anemia. On CT examination, no lymph node enlargement was noted anywhere in the chest or the abdomen. The other abnormal CT findings were splenomegaly with several low-attenuation areas and small amounts of ascites and pleural effusions.

IMP single-photon emission computed tomography (IMP-SPECT) (Fig 2) studies were performed by using a three-head rotating gamma camera (GCA-9300A/DI, Tokyo, Japan) with a low-energy, fan-beam, high-resolution collimator. Data were obtained by continuous rotation in a 128 $\times$ 128 matrix. The patient was blindfolded for 10 minutes before and after the injection. Data collection for SPECT images was initiated 20 minutes after the intravenous administration of 222 MBq I-123 IMP, which lasted for 1 minute. A filtered back-projection technique with Butterworth (cutoff frequency 0.10 cycles/pixel; order 8) and ramp filters were applied for image reconstruction. All data were collected at an attenuation of 0.146/cm by using the method of Chang. Image acquisition time was 20 minutes, and each section was 6.9 mm thick. Image sections were set up parallel to the orbitomeatal line. Regional CBF measurement was performed by obtaining single arterial blood sampling from the brachial artery 10 minutes after IMP infusion on the basis of theARG method (1). The distribution volume was fixed (V_d = 45 mL/mL), and the standard input function was referred to the data of Research Institute for Brain and Blood Vessels, in Akita, Japan. Three axial images through the midsection of the cerebellum and the Th and the BG and just above the lateral ventricles were selected to create irregular regions of interests for the measurements of rCBF in the cerebral cortical areas of each territory under anterior, middle, and posterior cerebral arteries, BG, Th, semioval center, cerebellum, and brain stem.

Initial IMP-SPECT on admission showed very high rCBF throughout the brain (Fig 2*A*). The values of rCBF in each region of interest were summarized in sequential studies (Table 1). After two courses of half-dose combination chemotherapy of CHOP (cyclophophamide, vincristine, doxorubicin, and prednisone), rCBF in IMP-SPECT (Fig 2B) decreased to a level within normal range. In late March 2000, after a total of six courses of combination chemotherapy, the patient left the hospital. On discharge, sIL-2R was reduced to a level of 100s, and the bone marrow biopsy showed myeloid hyperplasia without lymphoma. Five months later, sIL-2R was increased again to 1888 IU/mL, and bone marrow biopsy showed the presence

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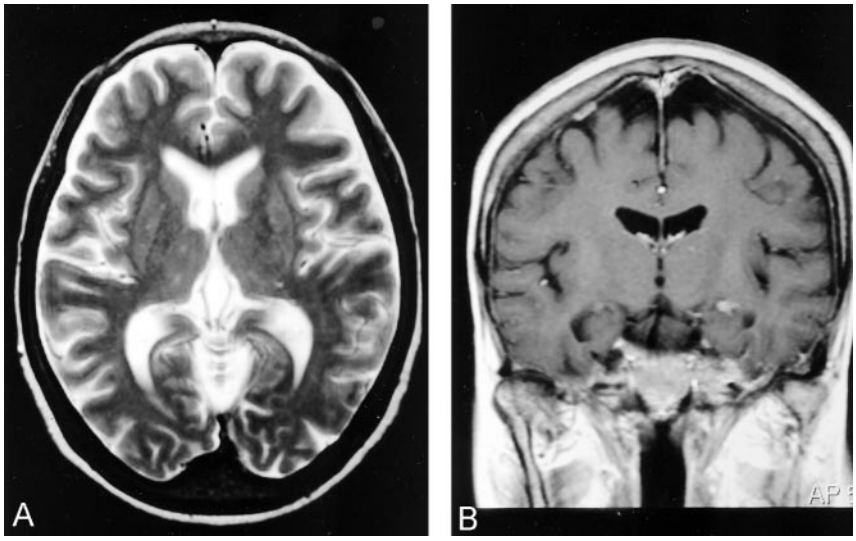

FIG 1. Images were obtained at the initial admission before chemotherapy began. Axial T2-weighted (3500/90) MR images (*A*) reveal minimum high-signal-intensity lesions in the both thalamus and putamen bilaterally. Coronal T1-weighted (458/14) MR image (*B*) shows that relatively thick meninges and bone marrow of the skull are enhanced after contrast material administration.

of lymphoma cells. After THP-COP (pirarubicin, cyclophophamide, vindesine, and prednisone) chemotherapy was carried out from September to November 2000, she received etoposide as an outpatient. On January 3, 2001, she was admitted for anorexia and progressive lethargy. Altered consciousness and mental status and progression of dementia were observed despite continuous THP-COP chemotherapy. On the morning of February 6, the day after chemotherapy, she was found to be right hemiparetic. Contrast-enhanced CT 6 hours after onset did not show any abnormal attenuation, except for increased vascular attenuation in the left cerebral hemisphere (Fig 3). On February 8, the patient demonstrated difficulty in speech. On February 9, approximately 2 hours after these symptoms disappeared and confusion was improved, IMP-PECT (Fig 2C) revealed high rCBF in the left cerebral hemisphere and the right cerebellum. On February 20, IMP-SPECT (Fig 2D) showed relatively high rCBF at similar degree in both the right and the left cerebral hemispheres. Nevertheless, several courses of chemotherapy could not suppress the progression of dementia, and the patient's condition continued to worsen. She died 17 months after her initial admission. The summary of sequential examination findings and chemotherapy protocol is shown in Table 2.

Autopsy revealed that vascular structures in brain parenchyma were prominent, and sporadic lesions with dark color in the cortex of the parietal area were suggestive of infarcts. Microscopic examination showed lymphoma infiltration in meninges, subarachnoid space, Virchow-Robin space of parenchyma, cerebral and cerebellar parenchyma, pituitary gland, lumina, and wall of the small vessels of the brain parenchyma (Fig 4). Lesions with dark color were gliosis and demyelinated, which are findings that are compatible with infarct. B-cell lymphoma was also identified in the blood vessels of the spleen, lungs, liver, kidneys, adrenal glands, and parametrium.

Discussion

Intravascular lymphoma (IVL)—also known as malignant angioendotheliomatosis, angiotropic large-cell lymphoma, or intravascular lymphomatosis (2, 3)—was first described in 1959 as "angioendotheliomatosis proliferans systemisata" (4). It is a rare, generally fatal, disease characterized by a multifocal proliferation of an aggressive type of non- Hodgkin lymphoma cells within the lumen of small blood vessels and commonly affects the CNS and the skin (2, 3). According to the literature, IVL has a predilection for patients in their 6th to 7th decades of life, with a male-female ratio of 1: 2—that is, the incidence in men is twice that in women. The most common manifestations are fever of unknown origin or intermittent fevers, skin rash, and changes of mental status. CNS involvement usually manifests an encephalopathy ranging from acute disorientation to rapidly progressive dementia and focal signs such as hemiparesis and myelopathy (5–7). Although any organ may be involved, those typically involved in lymphoma, such as the lymph nodes and bone marrow, are rarely enlarged or expanded by the neoplastic process (8). The involvement of hematopoietic organs is an uncommon feature, and bone marrow examinations in patients with IVL are usually nondiagnostic (5, 9). In addition, CSF analysis may show mild leukocytosis or an increased amount of protein, but cytologic results are negative for either finding in most patients (10). In the case presented here, however, not only was lymphoma infiltration found in the bone marrow and CSF, but also a CT scan of the abdomen suggested lymphoma involvement of the spleen on the initial admission. On laboratory examination, this case demonstrated, in addition to increased sIL-2R, all of nonspecific laboratory abnormalities such as anemia, increased CRP and serum LDH levels, and elevated erythrocyte sedimentation rate as described in most reports.

Recently, CT and MR findings of the brain have been reported in IVL. Williams et al (11) retrospectively reviewed MR imaging data in four cases of IVL. These MR findings included infarct-like lesions (n = 2), focal parenchymal enhancement (n = 3), dural-arachnoid enhancement (n = 2), and in one case, nonspecific, patchy foci of increased signal intensity in the white matter on long-TR images. All patients had multifocal lesions. The MR findings arose in part from vessels occluded by IVL, producing a wide spectrum of abnormalities that might range from multifocal nonspecific white matter changes to infarct-like

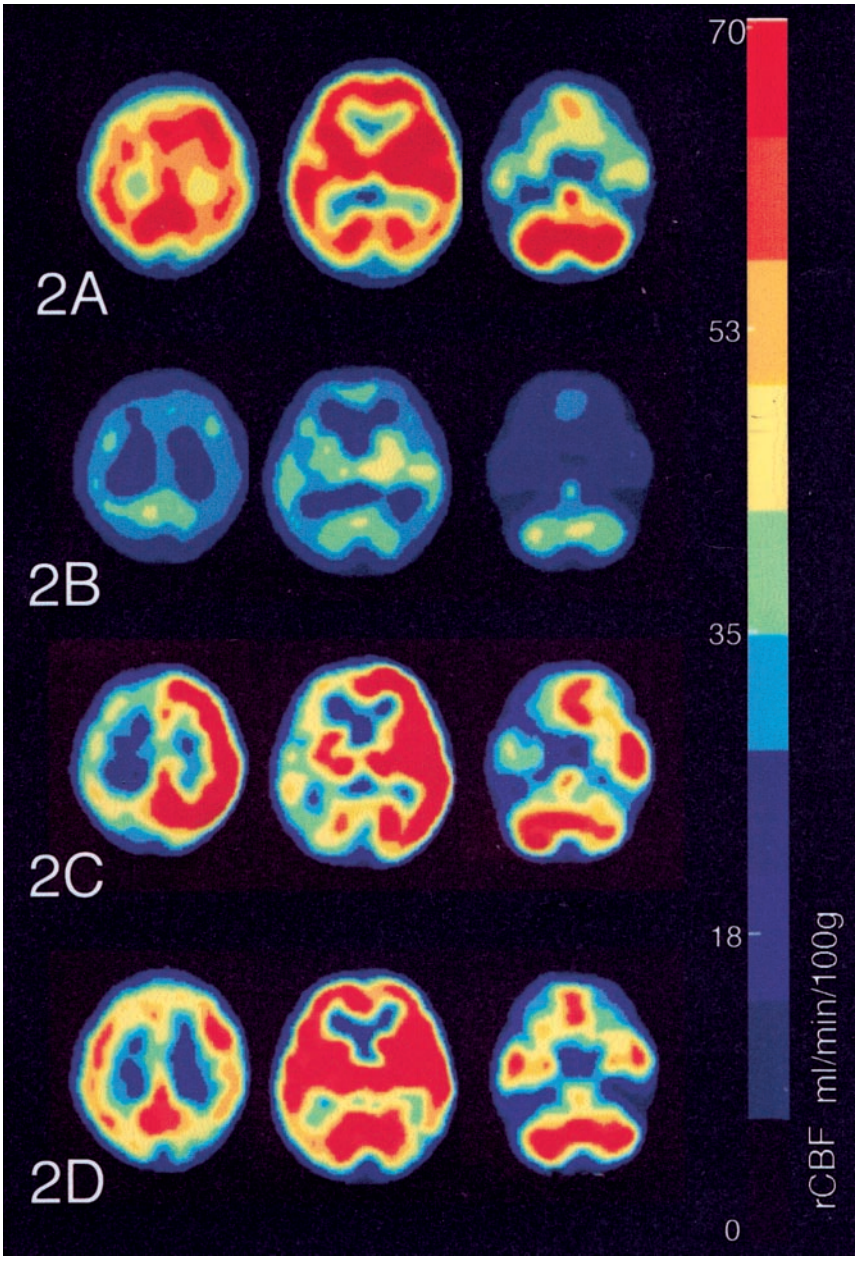

FIG 2. rCBF images at three different sections calculated by the I-123 IMP ARG method before the first course of chemotherapy (*A*), after the first course of chemotherapy (*B*), 2 hours after the recovery from the left hemiparesis (*C*), and 2 months before death (*D*) are shown. The same color scale is used to display quantitative rCBF images through four sequential I-123 IMP SPECT studies.

TABLE 1: Summary of the values of rCBF calculated by the I-123 IMP ARG method in sequential studies

	ACA		MCA		PCA		WM		BG		Cellrb	
Examination Date	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
November 30, 1999	54–60	57–65	58–62	59–63	54–67	48–60	40	45	79	87	64	66
December 20, 1999	30–36	33–37	33–36	33–37	35–40	32–38	22	21	42	48	42	40
February 9, 2001	35–45	48–60	36–43	58–70	36–46	49–61	29	42	45	54	56	51
February 20, 2001	45–60	43–56	47–59	46–68	50–59	46–56	36	27	56	67	64	65

Note.—ACA, cerebral cortex under anterior cerebral artery; BG, basal ganglia; Cellrb, cerebellum; MCA, cerebral cortex under middle cerebral artery; PCA, cerebral cortex under posterior cerebral artery; WM, semioval center.

lesions and that the MR appearance of IVL might also manifest as enhancing mass lesions, possibly predicting extra luminal spread of disease. Terae et al (12) summarized the latest MR findings of 33 patients with IVL as follows: 1) multiple hyperintense lesions on T2-weighted images or fluid-attenuated inversion recovery images mainly in the cerebral white matter; 2) infarct-like lesions involving the cortical and subcortical regions; 3) lacunar infarct-like lesions in the basal ganglia, thalami, and brain stem; 4) diffuse hyperintense lesions in the cerebral white matter on T2-weighted images; 5) contrast enhancement varies

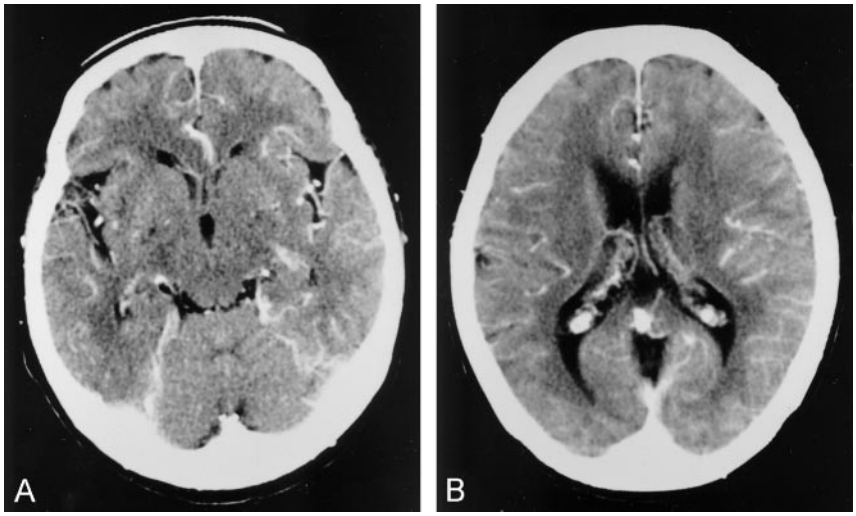

FIG 3. Images obtained on February 6, 2001, 10 hours after the onset of right hemiparesis. Postcontrast head CT shows that the vascular structures in the left cerebrum are enhanced as compared with those in the other side through the level of the third ventricle (*A*) and the body of the lateral ventricles (*B*).

TABLE 2: Summary of sequential examination findings and chemotherapy protocol

Date	Chemotherapy	Examination	Findings
November 26, 1999		MRI (Fig 1)	Minimum high intensity in the basal ganglia and thalamus on T2-weighted, dural/arachnoid enhancement with Gd-DTPA
November 30, 1999	CHOP	I-123 IMP (Fig 2*A*)	Very high rCBF throughout the brain before the first half-dose CHOP
December 20, 1999		I-123 IMP (Fig 2*B*)	rCBF decreased to a level within normal range after the two half-dose CHOP
February 5, 2001	THE-COP		
February 6, 2001		CT (Fig 3)	Increased vascular densities in the left cerebral hemisphere, 6 hours after the onset of right hemiparesis
February 9, 2001		I-123 IMP (Fig 2*C*)	High rCBF in the left cerebral hemisphere and the right cerebellum, 2 hours after the recovery from right hemiparesis
February 19–22, 2001	EPOCH		
February 20, 2001		I-123 IMP (Fig 2*D*)	Relatively high rCBF at similar degree in both the right and the left cerebral hemispheres.

from no enhancement to variable parenchymal enhancement, including either linear and punctuate, patchy, irregular, nodular, cortical, or periventricular enhancement, and meningeal enhancement such as dual, arachnoids, or pial enhancement; and 6) serial MR imaging might show development of new lesions or progression of existing lesions, fluctuation in size or number of the lesions in a relatively short period during corticosteroid therapy, or reduction of the lesion size after CHOP therapy. In the present case, however, initial MR imaging was essentially normal except for dural-arachnoid and postcontrast bone marrow enhancement at the time of the first admission. The reason there was no enhancement in the brain parenchyma with the initial MR imaging was mainly because the disease was at an early stage, and vessel occlusion had not occurred. The propensity for tumors to proliferate and remain within vascular spaces might have been minimal, whereas tumor infiltration in the wall of the small vessels and perivascular space of the brain parenchyma might have been slightly dominant; however, meninx and postcontrast bone marrow enhancement meant lymphoma infiltration. As the disease progresses, MR imaging must show the same cortical and white matter lesions as identified at autopsy.

Diffusion-weighted images, perfusion MR imaging, and MR angiography were not examined in this case. In the early stage of IVL, diffusion-weighted images might show a low apparent diffusion coefficient in an affected site, whereas perfusion MR imaging might reveal high rCBF and MR angiography might demonstrate segmental narrowing of the vessel, depending on the degree of infiltration of tumor.

The present case revealed very high rCBF on the first admission. After the first course of combination chemotherapy, the level of rCBF decreased to the normal range. Decreased rCBF of both cerebral hemispheres in brain SPECT was reported in a patient with IVL, accompanied by high-intensity lesions on T2-weighted in the brain and thoracic spinal cord. To our knowledge, there have been no reports describing high rCBF in IVL. IVL is known to mimic primary angiitis of the CNS (9), and angiography is nondiagnostic but suggest vasculitis (5). There were several reports that showed increased uptake of I-123 IMP or Tc-99m hexamethylpropyleneamine oxine (HMPAO) in patients with herpes simplex encephalitis, Japanese encephalitis, and viral encephalitis in acute to subacute phase (13–15). Also, it has been reported that early and delayed I-123 IMP uptake ratios comparing tumors with contralateral brain cor-

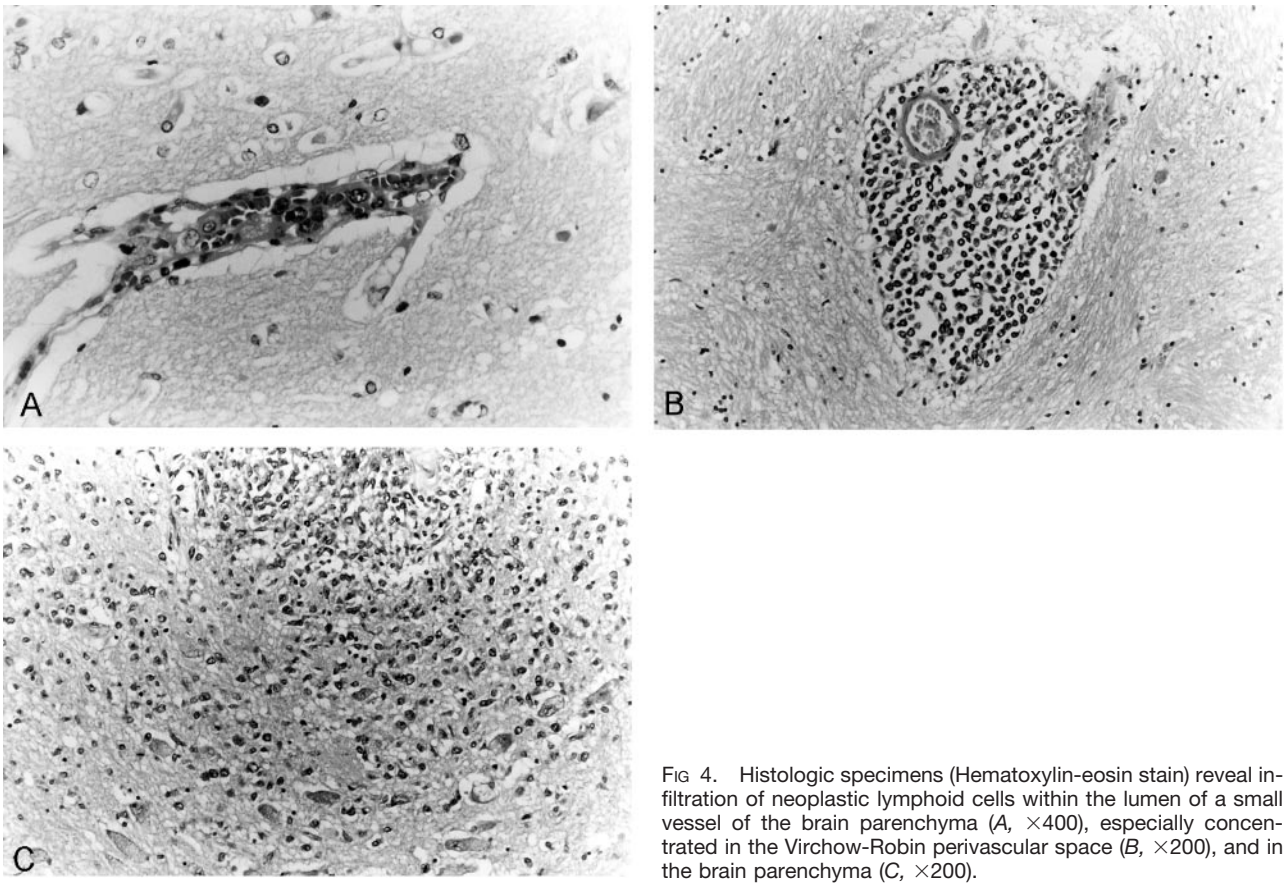

FIG 4. Histologic specimens (Hematoxylin-eosin stain) reveal infiltration of neoplastic lymphoid cells within the lumen of a small vessel of the brain parenchyma (*A,* ×400), especially concentrated in the Virchow-Robin perivascular space (*B,* ×200), and in the brain parenchyma (*C,* ×200).

tex (T/n ratio) of primary CNS lymphoma were significantly higher than those of nonlymphomatous tumors on both early and delayed images (16, 17). High rCBF observed in the present case may mean real high rCBF as the accumulation of lymphoma in itself like an inflammation process.

In the patient's final clinical stage, 15 months after onset, she suffered from right hemiparesis for several days. Contrast-enhanced CT showed increased vascular attenuation in the entire left cerebral hemisphere. Walls of the vessels or perivascular space were enhanced by contrast material or by the slow flow of contrast material, because proliferation of tumor cells in the lumen of the vessels may have caused increased vascular attenuation. IMP-SPECT revealed high rCBF in the left cerebral hemisphere and the right cerebellum immediately after the symptom had abated. Increased I-123 IMP activity that was compatible with reperfusion hypereamia in a patient who suffered a subacute stroke and increased Tc-99m HMPAO in a cardioembolic mechanism of stroke have been reported (18, 19). It has been suggested that tumor cell infiltration to the left cerebral parenchyma induced the right hemiparesis and increased I-123 IMP uptake in the left cerebral hemisphere. Also reperfusion hypereamia was assumed after transit vascular occlusion because of tumor cells or dead tumor cells after chemotherapy. We could not, however, explain the reason why the half of the brain was affected.

Conclusion

As the disease progresses, MR imaging may reveal high-signal-intensity lesions on T2-weighted images. Elevated LDH or sIL-2R levels can be a good indicator of IVL; however, diagnosis of IVL remains difficult, especially at the early stage. Although the exact reason for high rCBF in IVL is still unknown, increased rCBF in SPECT may be helpful to diagnose early-stage IVL, in addition to other clinical findings, before cranial MR images can present nonspecific hyperintense lesions. In this case, effective chemotherapy could not suppress the progression of dementia, and autopsy revealed aggressive infiltration of tumor cells into the brain parenchyma. To improve the prognosis of the IVL, an accurate and early diagnosis is needed as soon as possible.

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