INTRODUCTION

Central nervous system lymphoma (CNSL) typically manifests as a well-demarcated mass with strong and homogenous gadolinium enhancement in the periventricular and/or superficial region. We report a case of central nervous system lymphoma (CNSL) manifesting as multiple white matter lesions with non-tumorous patchy or ring-like enhancement and partial spontaneous resolution on magnetic resonance imaging (MRI). Such findings are unusual and could lead to misdiagnosis without pathological evaluation.

CASE REPORT

A 55-year-old man visited our hospital because of headache and insomnia persisting for 2 months. He had a medical history of Clinical Stage IA left tonsillar diffuse large B cell lymphoma (DLBCL) treated with 3 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and radiation therapy, and a recurrence in the left inguinal lymph nodes treated with 3 cycles of cyclophosphamide, cytosine arabinoside, etoposide, and dexamethasone (CHASE) and autologous bone marrow transplantation 7 months later. He had not suffered from recurrence in 9 years.

Initial non-enhanced MRI revealed multiple patchy hyperintense lesions on T2WI and fluid-attenuated inversion recovery (FLAIR) images in the cerebral white matter (Figs. 1a, 1b). These lesions were isointense on diffusion-weighted images (DWI) and iso- to slightly hyperintense on apparent diffusion coefficient (ADC) map (Figs. 2a, 2b). Because of indeterminate correlation between the patient's symptoms and imaging findings, which were not only nonspecific but also atypical for leukoaraiosis, follow-up MRI with gadolinium contrast media was performed 4 weeks later. Abnormal lesions in the white matter in the posterior left lateral ventricle, bilateral frontal white matter, and right
centrum semiovale were found to have partially resolved spontaneously, but other lesions had deteriorated with further involvement of the splenium of the corpus callosum (Figs. 1c, 1d). A part of these deteriorated lesions showed hyperintense on DWI without signal reduction on ADC map (Figs. 2c, 2d) and partial patchy or ring-like gadolinium enhancement (Figs. 3a, 3b). Due to deterioration of the clinical symptoms and imaging findings, he was admitted to undergo further examinations. MRI taken 6 weeks from initial examination showed further deterioration (Figs. 1e, 1f) with patchy or ring-like partial gadolinium enhancement (Figs. 3c, 3d). Although the DWI hyperintense lesions also deteriorated, there was no signal reduction on ADC map (Figs. 2e, 2f). Abnormal lesions which had resolved spontaneously on FLAIR images showed isointensity on DWI with slight hyperintensity on ADC map and no enhancement through serial MRI scans. Though contrast-enhanced MRI taken 8 weeks from initial examination for stereotactic biopsy showed deterioration, some enhanced lesions had partially vanished (Figs. 3e, 3f). Concomitantly, symptoms of irritability, dysmnesia and lethargy developed. Blood test showed no abnormalities, including a normal level of soluble interleukin-2 receptor (sIL-2R). Spinal fluid examination showed a slightly high level of protein (73 mg/dL), normal cell count and negative cytology. Bone marrow aspiration, bone marrow biopsy and skin biopsy showed no malignancy.

Although intravascular lymphomatosis (IVL) and vasculitis were suspected from radiological findings, other examinations including sIL-2R, skin biopsy and cerebrospinal fluid cytology did not reveal specific findings for diagnosis. Stereotactic biopsy from the left frontal lobe white matter lesion that had deteriorated with patchy enhancement (Fig. 3f) revealed DL-
BCL (Figs. 4a, 4b). Though the left tonsil lymphoma and CNSL were both DLBCL, the clonal relationship between the primary tumor and the late relapse could not be proven with molecular methods because the original tumor specimen was not available. Thus, second primary lymphoma cannot be excluded. Throughout the clinical course, no corticosteroids or any other drugs were administered, except for benzodiazepines and related drugs for insomnia. CT was performed only once on the day before the third MRI scan.

After treatment with chemotherapy and radiotherapy, CNSL relapsed 14 months later. He then underwent allogeneic bone marrow transplantation and has been treated as an outpatient for the last 3 months.

**DISCUSSION**

Lymphomas can arise within the Central nervous system (CNS) as primary CNS lymphoma (PCNSL) typically involving the brain and less often the leptomeninges, eyes, and spinal cord. In contrast to PCNSL, secondary CNS lymphoma (SCNSL) is considered to originate as quasi metastasis from systemic lymphoma spreading to the CNS. In systemic DLBCL, the relapse rate 2 years after diagnosis is only 2.2% per year [3]. Very late relapses after more than 10 years in complete remission have only been documented in a few case series totaling less than 20 [3-6], the longest time in complete remission being 28 years [7].

Parenchymal metastases from non-Hodgkin’s lymphoma (NHL) often appear as single or multiple enhancing lesions and can be accompanied by leptomeningeal metastases [8]. The parenchymal lesions may have a periventricular and/or superficial location. Unenhanced computed tomography typically reveals hyper- or iso-attenuated lesions, and virtually all lesions show contrast enhancement. On unenhanced T1-weighted images (T1WI), lesions are typically hypointense or isointense, and on T2WI, isointense to hyperintense but often hypointense to the gray matter, and on DWI typically hyperintense with signal reduction on ADC map [2]. This hypointensity on T2WI as well as low ADC values has been attributed to a high nuclear to cytoplasmic ratio and to high cellularity of...
these tumors [2]. In our case, diffusion restriction, which is commonly found in lymphoma, was not present. The high signal intensities on DWI were considered to be due to T2 shine-through effect, which could be detected by the ADC-map showing normal to slightly high water diffusion. They might also be due to inflammatory mechanisms, such as those that cause vasogenic edema. On deteriorating lesions, the low

**Fig. 3.** a-f. Sequential changes of contrast enhancement pattern on T1WI. MRI taken from 4 weeks (a, b), 6 weeks (c, d), 8 weeks (e, f) after initial noncontrast examination are shown. MRI taken 4 weeks after initial noncontrast examination shows ring-like enhancement in the left frontal white matter (arrowhead, Fig. 3a). It deteriorate 2 weeks later (arrowhead, Fig. 3c) and resolve another 2 weeks later (arrowhead, Fig. 3e). Though patchy enhancement in the right frontal white matter (arrow, Fig. 3c) and right centrum semiovale (arrow, Fig. 3d) deteriorate, enhancement in posterior part of the left centrum semiovale (arrowhead, Fig. 3d) resolve 2 weeks later (arrowhead, Fig. 3f). A needle biopsy of the left frontal white matter lesion (arrow, Fig. 3f) was performed.

**Fig. 4.** a, b. Histopathological findings of the left frontal white matter lesion. Hematoxylin-eosin staining (original magnification $\times 200$) (a) showing scattered infiltration of lymphoma cells with a high nucleoplasmic ratio in the white matter. Immunohistochemical studies (b) showing lymphoma cells positive for CD20 (original magnification $\times 200$).
cellularity, as proven by the surgical specimen of the CNS lesion, may affect the intensity on DWI and ADC-map. The most common enhancement pattern is a homogenous nodular pattern. A perivenular or infiltrative pattern is less common. Patchy and ring-like enhance-momous nodular pattern. A perivenular or infiltrative map. The most common enhancement pattern is a ho-

CNS lesion, may affect the intensity on DWI and ADC-cellularity, as proven by the surgical specimen of the SCNSL; this similarity makes it impossible to discriminate these 2 entities on the basis of neuroimaging [2].

In our case, partial resolution of high intensity les-

ons on FLAIR images and enhanced lesions might have been the result of inflammation improvement rather than tumor regression. Alderson et al. [10] created the term “sentinel lesions” for inflammatory de-myelinating brain lesions preceding PCNSL that show spontaneous or corticosteroid-induced resolution on contrast-enhanced MRI. In most cases, histopathologi-
cal analysis of the “sentinel lesions” showed a cellular infiltrate predominantly consisting of T lymphocytes with only rare B lymphocytes [10,11]. Lymphoma cells may develop accidentally due to an intrathecal clonal proliferation among normal B-lymphocytes within the context of an inflammatory CNS disease becoming manifest in “sentinel lesions”. On the other hand, “sen-
tinel lesions” may be the first immunological response mounted against a developing CNS lymphoma, which may escape diagnosis in an inflammatory environment [12]. This phenomenon could explain the spontaneous resolution in our case. Matosevic et al. [13] reported a case of PCNSL showing progressive leukoencepha-

lopathy, which was similar to our case. The leukoen-
ccephalopathy was caused by lymphoma-related occlusion of small-sized and medium-sized arteries and diffuse infiltrating lymphomas, which gave rise to microglia and T cell activation resulting in inflammatory white matter damage [13]. In our case, although there was no evidence of invasion into vessels on the small brain specimen, the lymphomatous involvement of the vessels might explain the emergence of patchy white matter lesions.

Regression of malignant lymphoma with corticos-

steroids is well known [14]. Spontaneous regression of lymphoma has been reported for systemic low-grade lesions and leptomeningeal lymphoma as a primary or secondary disease [15]. However, regression without steroid therapy is extremely rare in PCNSL [16]. To the best of our knowledge, spontaneous regression of SCNSL has never been reported. The mechanism may be that natural killer cells triggered by an immune re-
sponse to viral infection or biopsy reduced the tumor burden [16].

In our case, brain MRI showed multiple patchy white matter lesions with hyperintensity on T2WI and patchy or ring-like partial gadolinium enhancement. The lesion showed a partial spontaneous resolution. Furthermore, progressions of other lesions were too rapid for a neoplastic disease. These non-tumorous find-

ings are rare and similar to vasculitis or IVL, so it is quite difficult to make a differential diagnosis without histological examination. In these cases, brain biopsy should be performed for rapid and appropriate treatment.

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