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LETTER TO THE EDITOR

Primary CNS CD45-Depleted T-Cell Lymphoma: The First Pathologically Confirmed Case

Tamaki Morisako, MD, Yukiko Shishido-Hara, MD, PhD, Tohru Inaba, MD, PhD, Hayato Takeuchi, MD, PhD, Aya Miyagawa-Hayashino, MD, PhD, Yoshinori Kodama, MD, PhD, Yoshinobu Takahashi, MD, PhD, Eiichi Konishi, MD, PhD, and Naoya Hashimoto, MD, PhD

From the Department of Neurosurgery (TM, HT, YT, NH); Department of Pathology and Applied Neurobiology (YS-H, YK); Department of Infection Control & Laboratory Medicine (TI); and Department of Surgical Pathology, Kyoto Prefectural University of Medicine, Graduate School of Medical Sciences, Kyoto, Japan (AM-H, EK)

Send correspondence to: Yukiko Shishido-Hara, MD, PhD, Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine, Graduate School of Medical Sciences, 465 Kajii-cho Kawaramachi-Hjirokoji, Kamigyo-ku, Kyoto 602-8566, Japan; E-mail: shiyuki@koto.kpu-m.ac.jp

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To the Editor:

Primary central nervous system lymphoma (PCNSL) is usually a high-grade B-cell neoplasm of the large cell type (diffuse large B-cell lymphoma [DLBCL]), composed of tumor cells with apparent cytological atypia. DLBCL cells display a B-cell surface marker, CD20, as well as CD45, also known as leukocyte-common antigen. Surface expression of CD45 is highly specific to hematopoietic cells; therefore, it may be a useful diagnostic marker to differentiate PCNSL from glioma or metastatic carcinoma in the CNS. A few reported cases of systemic B-cell lymphoma or leukemia lacked surface expression of CD45 (1–3), and an extremely rare primary CNS CD45-negative B-cell lymphoma has also been described (4).

Primary CNS T-cell lymphoma (PCNSL-T) is rare; a study from western countries reported that only 8 cases of T-cell malignancies were involved in 370 PCNSL cases (2%) (5). Studies focused on the pathology of PCNSL-T are limited. In an elaborate pathological analysis, among 18 PCNSL-T cases, 15 of these were classified as peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), 2 as anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL), and one as ALK-positive ALCL (6). Among 15 PTCL, NOS cases, 14 showed neoplastic T cells with small-to-medium-sized nuclei, which made identification of neoplastic and nonneoplastic perivascular T cells more difficult. Consequently, inflammatory demyelinating diseases would become a likely differential diagnosis in some cases (7).

A 79-year-old male patient was admitted to our hospital with right hemiparesis. Neurological examination revealed right hemisensory disturbance and slight dysphasia. His medical history included diabetes mellitus and glaucoma but these conditions were well-controlled. Both blood and cerebrospinal fluid tests were unremarkable. They included a soluble interleukin-2 receptor (sIL-2R) concentration of 303 U/mL (normal range: 145–519 U/mL). Magnetic resonance imaging (MRI) demonstrated a solitary, contrast-enhancing tumor with surrounding edema located in the left parietal lobe (Fig. 1A–D). ^{18}F-fluoro-deoxyglucose positron emission tomography (FDG-PET) of the whole body did not reveal any detectable malignant lesions, except in the brain (Fig. 1F, G). Consequently, PCNSL was suspected, although a differential diagnosis of glioblastoma was also put forward. Since a morphological deterioration of the neighboring gyrus was not apparent, the possibility of demyelinating diseases or vasculitis was ruled out. One week after hospitalization, the patient's right hemiparesis progressed and MRI showed enlargement of the existing lesion (Fig. 1E). Partial resection was performed, and cytological examination revealed atypical lymphoid cells with irregularly enlarged nuclei. Flow cytometry (FCM) analysis demonstrated that >80% of the analyzed cells expressed pan-T-cell antigens (CD2, CD3, CD5, and CD7) as well as the T-cell receptor (TCR) αβ chain, suggesting a mature T-cell phenotype with an overall dim CD4 expression. Approximately 16.3% of the examined cells were also double-positive for CD2 and CD56. In contrast, tests for all B-cell markers (CD19, CD10, and CD20) and the myeloid marker (CD33) were negative. Unexpectedly, the tumor cells depleted of surface expression of CD45 (Fig. 1H).

Pathological examination revealed a tumoral lesion of high cellularity, consisting of large severely atypical cells with irregular or pleomorphic nuclei. Mitotic figures were also seen (Fig. 2A). The tumor cells diffusely and densely

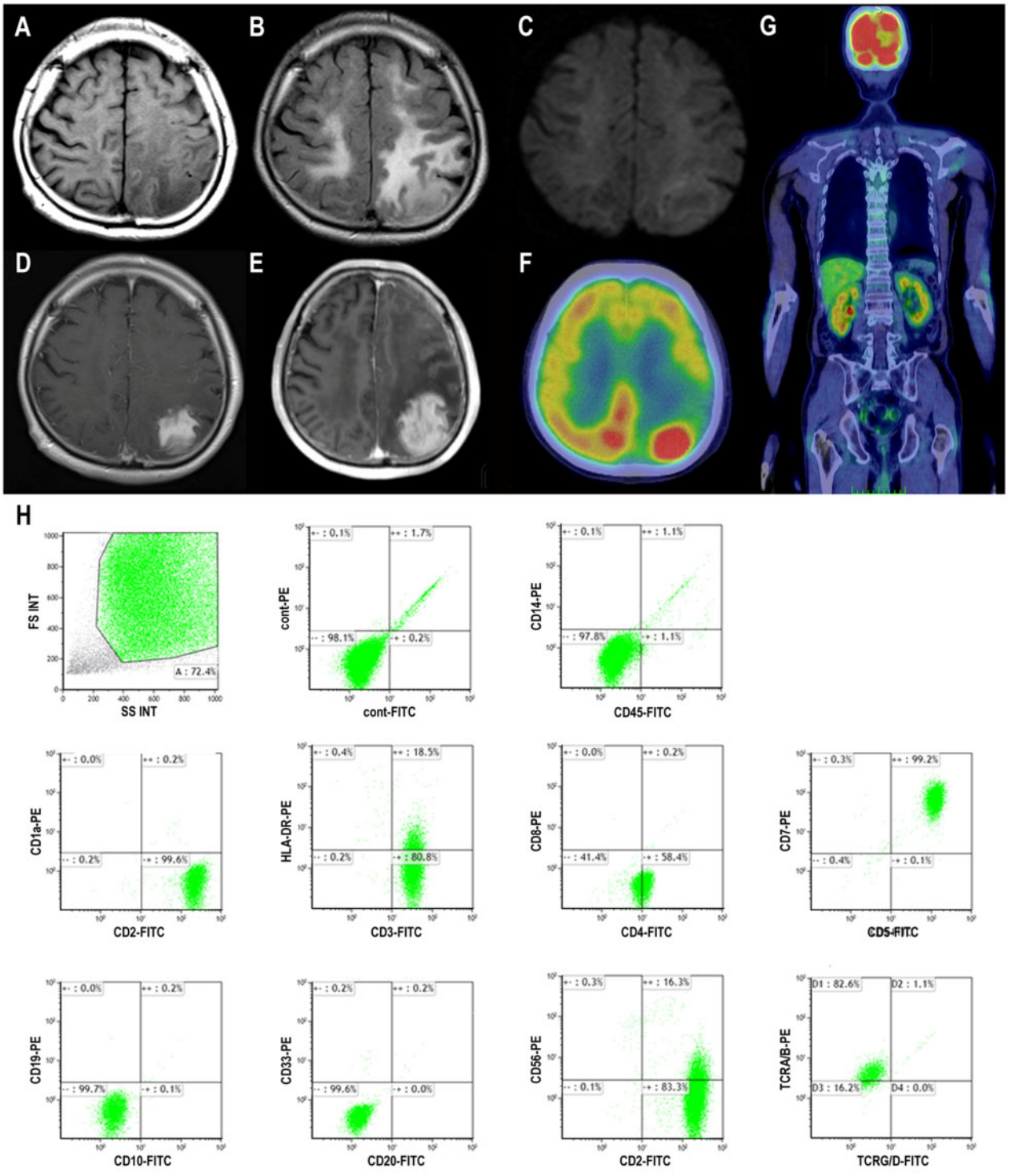

FIGURE 1. Brain MRI, FDG-PET images, and FCM analysis. **(A)** T1-weighted image showing a hypointense mass lesion. **(B)** Fluid-attenuated inversion-recovery (FLAIR) image showing the mass lesion with mildly high intensity and surrounding edema. **(C)** Diffusion-weighted image showing a mixed intense lesion. **(D)** Gadolinium (Gd) enhanced T1-weighted image showing a mass lesion that was irregularly contrasted, on admission. **(E)** Gd-enhanced T1-weighted image taken one week after hospitalization, when the patient showed clinical progression with enlargement of the mass lesion. **(F, G)** FDG-PET did not reveal any detectable malignant lesions except for that in the brain. **(H)** Surface marker analysis of tumor cells using FCM. The tumor cells were CD14(–), CD45(−), CD1a(+), CD2(+), HLADR(+, partially), CD3(+), CD8(−), CD4(+, dim), CD7(+), CD5(+), CD19(–), CD10(−), CD33 (–), CD20(−), CD56(+, partially), CD2(+), and TCRαβ (+).

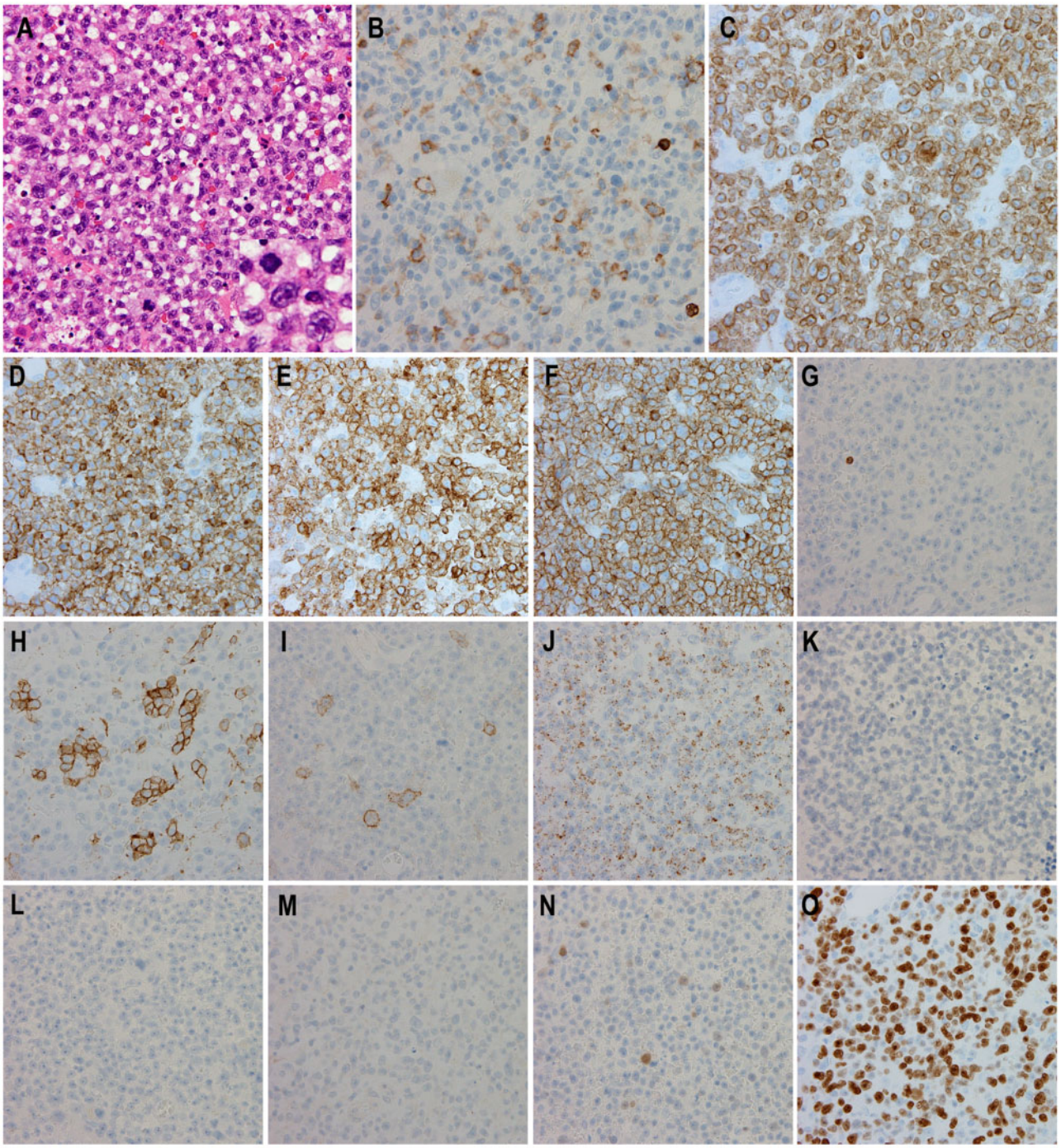

FIGURE 2. Pathological findings. **(A)** Hematoxylin and eosin staining showing lymphoma cells with large nuclei of severe atypia. High-power view of tumor cells is shown in inset. **(B–O)** Immunohistochemistry revealing a tumor phenotype that was consistent with FCM. **(B)** CD45(−), **(C)** CD3(+), **(D)** CD5(+), **(E)** CD7(+), **(F)** CD4(+), **(G)** CD8(−), **(H)** CD56(+, partly), **(I)** CD30 (+, partly), **(J)** granzyme B(+), **(K)** EBER-ISH(−), **(L)** CD20(−), **(M)** CD10(−), **(N)** MUM-1 (+, partly), and **(O)** MIB-1 labeling index (>70%).

infiltrated the brain parenchyma and subarachnoid space. An angiocentric infiltration pattern was also seen. Morphological features were similar to DLBCL, but the immunohistochemistry (IHC) reflected T-cell malignancy. Consistent with FCM results, the tumor cells depleted CD45-expression but evidently positive for CD3, CD5, and CD7 (Fig. 2B–E). Most tumor cells were positive for CD4 but not for CD8 (Fig. 2F, G). Expression of CD56 and CD30 were partly seen (Fig. 2H, I). The relatively large number of CD56-positive cells suggested a resemblance to natural killer T (NK/T) cell lym-

phoma, but while most cells were positive for granzyme B, Epstein Barr (EB) virus encoded small RNA-in situ hybridization (EBER-ISH) did not indicate EB virus infection (Fig. 2J, K). All markers of B-cell lineage, CD10, CD20, and MUM-1 tested negative. The markedly high MIB-1 labeling index reflected an aggressive lymphoma.

The patient did not show any lymphomatous lesions other than that in the CNS; therefore, he was diagnosed as PCNSL-T. He was referred to hematologists and was given high-dose methotrexate (MTX) and MPV (MTX, procarbazine, vincristine) therapy. His clinical conditions improved, and he was transferred to a different hospital for rehabilitation. However, 6 months after surgery, he experienced a relapse in his skin without recurrence of an intracranial tumor. The pathology revealed the T cell lymphoma, of which histological features were the same as those in the CNS. He received reinduction of chemotherapy, but eventually died of pneumonia, 8 months after surgery.

The occurrence of PCNSL-T is extremely rare. Due to the limited number of cases, PCNSL-T has not yet been fully subclassified on the basis of pathological analyses. Many cases have previously been classified as PTCL, NOS, with tumor cells often showing small-to-medium sized nuclei of low-grade appearance. Although the cases are few in number, both ALK-positive and ALK-negative, primary CNS ALCL have been reported (8, 9). The lymphoma cells show large nuclei of severe atypia, suggesting the presence of aggressive features. Furthermore, primary CNS NK/T-cell lymphoma may also occur (10–12). Therefore, PCNSL likely conform to variable classifications although the presence/absence of CD45 molecules on the neoplastic T cells has not yet been documented.

Although absent cell surface expression of CD45 has been described in acute lymphoblastic leukemia (ALL), B-lymphoblastic leukemia, and DLBCL (1, 3, 13, 14), CD45-depleted T-cell neoplasms have been rarely reported regardless of the tumor locations. In this examined case, coexistence of nontumoral inflammatory cells may influence the precise data of FCM, but IHC displayed evident CD45 depletion on most neoplastic cells. The neoplastic T cells showed large nuclei with severe atypia, accompanied by high-level mitotic activity. The morphological features were distinct from those of PTCL but somewhat similar to those seen in ALCL. The presence of CD30-positive cells is a common feature. But CD30-positive cells represented only $<10\%$ of tumor cells, that is, most tumor cells were CD30-negative. Expression of CD56 was apparent in some of the tumor cells examined by IHC, and corresponding results were also obtained by FCM ($\sim$16.3% of cells). The presence of CD56-positive cells suggests a resemblance to NK/T-cell lymphoma, but EB virus infection could not be detected by EBER-ISH. Although a weak CD4 surface signal caused the lower positivity with standard threshold by FCM, IHC distinctively presented that most lymphoma cells are CD4-positive, but CD8-negative, with αβ-type TCRs. Expression of terminal deoxynucleotidyl transferase (TdT) was also examined, and its negativity indicated mature T cell neoplasm, but not T-ALL. Depletion of CD45 surface expression is seen in 4% of PTCL (15), but this is the first description of CD45 depletion in a CNS T cell lymphoma. Although the origin of the neoplastic T cells remains unknown, this tumor did not meet the existing criteria described in the WHO classification (2016) of Tumors of the Central Nervous System. This important case may indicate the presence of a new type of PCNSL-T.

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