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Case Report

Accurate Detection of Tumor Infiltration by ^{11}C-Methionine Positron Emission Tomography in a Patient with Central Nervous System Intravascular Lymphoma: A Case Report

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Keywords
Intravascular lymphoma · Central nervous system · ^{11}C-methionine · Positron emission tomography · Stereotactic biopsy

Abstract
Intravascular lymphoma (IVL) is a rare and clinically devastating subtype of extranodal diffuse large B-cell lymphoma with a distinct presentation. Diagnostic difficulty derives from marked variability in clinical presentations and nonspecific laboratory and radiological findings, especially when central nervous system (CNS) symptoms are the only manifestation. Establishing the diagnosis premortem thus remains a major challenge. We describe a 70-year-old male with CNS IVL. He presented with acute onset of neurocognitive impairments. Diffusion-weighted magnetic resonance imaging (MRI) showed multiple high-intensity areas suggesting occlusive cerebrovascular disease due to emboli, but extensive investigations detected no embolic sources. Intracranial neoplasm was included in a differential diagnosis based on elevated serum lactate dehydrogenase and interleukin 2 receptor levels. Gadolinium-enhanced MRI or 18-fluorodeoxyglucose positron emission tomography (PET) failed to demonstrate specific find-

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ings leading to a definite diagnosis, while ^{11}C-methionine PET (MET-PET) distinctively demonstrated an area of focally increased MET uptake in the frontal cortex, suggesting the extent of tumor infiltration. Stereotactic biopsy was conducted under MET-PET imaging guidance and immunohistological examinations confirmed the proliferation and aggregation of CD20-positive lymphoma cells within the lumina of small blood vessels. The findings of the present case first suggest that MET-PET may provide important information on the diagnosis of CNS IVL and on the selection of the optimal site for brain biopsy. Further investigation is necessary to clarify whether positive findings on MET-PET are truly specific and pathognomonic for CNS IVL.

Introduction

Intravascular lymphoma (IVL) is a rare and clinically devastating subtype of extranodal diffuse large B-cell lymphoma with a distinct presentation, which is characterized by the selective growth of tumor cells in the lumina of small vessels with relative sparing of the surrounding tissue in the current World Health Organization classification [1]. The cause of its affinity for the vascular bed remains unknown. Its prevalence was estimated to be less than one person per million in a population-based study [2]. This disease entity has a high incidence of central nervous system (CNS) involvement at diagnosis [3]. Diagnostic difficulty derives from marked variability in clinical presentations and nonspecific laboratory and radiological findings, especially when CNS symptoms are the only manifestation. Accurate diagnosis is often delayed and is frequently determined at autopsy [4]. Establishing the diagnosis premortem thus remains a major challenge. ^{11}C-methionine positron emission tomography (MET-PET) studies have provided promising results in the field of neuro-oncology, based on high amino acid uptake by tumor tissue with low uptake by normal brain tissue, resulting in an enhanced tumor-to-background contrast. To date, however, MET-PET has not been shown to be useful for the detection of CNS IVL due to the rarity of this disease. The present study aimed to assess the adjunctive role of MET-PET as a guide for stereotactic biopsy, leading to early histopathological diagnosis of CNS IVL.

Case Report

The patient was a 70-year-old man who had visited our hospital for a periodic health checkup 6 months earlier, and the results of the blood tests at that time had been normal. He visited us again because of acute onset of memory disturbance, attention deficit, and gait disturbance. Neurological examination showed depressive mood, neurocognitive impairment, and unsteady gait. Skin inspection disclosed no particular findings. Brain diffusion-weighted magnetic resonance imaging (MRI) showed multiple scattered high-intensity areas predominantly in the left frontal subcortex and the right posterior cingulate gyrus (Fig. 1a). Fluid-attenuated inversion recovery (FLAIR) images were consistent with those in diffusion-weighted images (Fig. 1b). Acute embolic cerebral infarction was first suspected and an embolic source was thoroughly explored, but none was detected. His symptoms gradually worsened and the lesions on MRI increased. On cerebrospinal fluid assay, the cell count was 5/mm^3 (lymphocytes only), and no malignant cells were detected, while cerebrospinal fluid glucose and protein levels were 66 mg/dL (normal 40–70 mg/dL) and 118 mg/dL (normal <40 mg/dL), respectively. Whole-body computed tomography scans were negative for metastases. Lab-

oratory workup showed serum lactate dehydrogenase to be consistently elevated, rising from 337 up to 522 U/L (normal 115–245 U/L). Serum interleukin 2 receptor levels were markedly elevated at 1,090 U/mL (normal 145–519 U/mL). Beta-2 macroglobulin was 4.1 mg/L (normal 1.0–1.9 mg/L). Under a suspected diagnosis of CNS IVL, the patient underwent a random skin biopsy, which failed to yield any positive findings. He further underwent gadolinium-enhanced MRI, 18-fluorodeoxyglucose (FDG)-PET, and MET-PET. No corresponding enhancement was observed on gadolinium-enhanced MRI (Fig. 1c). FDG-PET was also inconclusive, revealing an FDG uptake decrease in the affected area corresponding to the site of high intensity on FLAIR images (Fig. 1d), which was considered to reflect parenchymal hypometabolism secondary to regional blood flow decrease. Extracranial foci were not detected on FDG-PET. In contrast, MET-PET showed a unique MET uptake increase in the left frontal cortex with a standardized uptake value of 2.30 and a lesion/normal ratio of 1.35 (Fig. 1e). Based on our analysis of all collected data from laboratory and neuroimaging tests, CNS IVL was the most likely diagnosis, and a stereotactic biopsy was thus attempted. A surgical map was generated employing the Leksell SurgiPlan software (Elekta Instruments, Stockholm, Sweden). After image coregistration with MRI and MET-PET images obtained prior to the procedure, the biopsy target and corridor were set in such a way as to pass through the areas of MET hyperaccumulation (Fig. 2). Stereotactic biopsy was then performed using the Leksell G stereotactic frame (Elekta Instruments) under local anesthesia supplemented with adequate sedation. Six columnar histopathological specimens were obtained along the planned biopsy corridor. Hematoxylin and eosin staining demonstrated marked proliferation of atypical lymphoid cells in the lumina of small vessels with absence of malignant cells in the surrounding tissue (Fig. 3). Immunohistochemical examinations revealed that the tumor cells were strongly positive for CD20 and MUM1 (Fig. 3), weakly positive for CD10, and negative for CD3 and CD5. Thus, the histological diagnosis was established as intravascular large B-cell lymphoma in the CNS 3 weeks after clinical presentation. The patient was referred to the hematology department of our university hospital and is presently receiving therapy.

Discussion

IVL can affect almost any organ and its manifestations are heterogeneous, thus often making a clinical diagnosis challenging. As patients with CNS IVL frequently present with dementia and/or stroke-like symptoms [3], CNS IVL is not even included in the initial differential diagnosis. There are no pathognomonic neuroradiological findings for CNS IVL. Brain MRI sensitively shows abnormalities, particularly multiple metachronous cortical or subcortical lesions that have high intensities on diffusion-weighted and FLAIR images, suggestive of small-vessel ischemia or demyelination [5]. The next common alternative diagnosis considered in IVL cases with these MRI findings is CNS vasculitis [6]. Magnetic resonance spectroscopy was reportedly insufficient for diagnosing IVL of the CNS [7]. Thus far, two studies from Japan of FDG-PET applied to CNS IVL have been published. Higashiyama et al. [8] reported the usefulness of FDG-PET for applications in biopsy and diagnosis of CNS IVL. On the other hand, the conclusions of Kawai et al. [7] were quite different, with FDG-PET failing to show the presence of tumor lesions or to clarify tumor characteristics. In the present case, FDG-PET showed hypoaccumulation in the high-intensity areas on FLAIR images which seemed compatible with ischemic lesions and was rather unlikely to represent neoplasms. Although MET-PET is recognized as a viable diagnostic option in the field of neuro-oncology, few evaluations of MET-PET for the imaging of CNS IVL have as yet been reported. In a case reported by Kawai et

al. [7], MET-PET images showed no significant increase in MET uptake in the lesions. In the present case, MET-PET demonstrated significant hyperaccumulation in the left frontal cortex, which clearly indicated a brain tumor but not normal or ischemic brain tissue. Although the superiority of MET-PET over other imaging modalities, including FDG-PET, needs to be verified by studies with a larger number of patients, our case clearly showed that CNS IVL lesions can present with high uptake on MET-PET, findings which should lead to further investigation to obtain a correct diagnosis.

Brain biopsy is the gold standard for diagnosing CNS IVL [7]. Stereotactic procedures are relatively safe and less invasive than diagnostic methods such as craniotomy and are applicable even to elderly patients and those in poor overall condition. As to the procedure, how to determine the optimal biopsy trajectory and target is critically important because the very limited specimens obtained with biopsy forceps carry a risk of false-negative results. MET-PET demonstrated hyperaccumulation in the left frontal cortex, which was not seen with gadolinium enhancement, and showed a slight shift from the subcortical high-intensity area seen on FLAIR images in the present case. This geometrical gap between neuroimaging modalities was a matter of debate when deciding the biopsy target. Our neurosurgical team eventually set a target in the subcortex through the left frontal cortex corresponding to MET hyperaccumulation (Fig. 2) because it was the only area with evident malignant cells. The FDG hypoaccumulation in the left frontal subcortex could have been due to a decreased regional blood supply from the cortex to the subcortex. Furthermore, a significant increase in MET accumulation was observed only in a single area, although MRI revealed intensity changes in multiple areas. Why did some areas involving lymphoma cells show hyperaccumulation, while other areas showed no change on MET-PET? We speculate that one possible reason may be the difference in the density of viable lymphoma cells filling vessel lumina. The second reason may be extravascular growth of lymphoma cells. The incidence of extravascular infiltration of lymphoma cells is reportedly relatively high in CNS IVL [9], and there might be hyperaccumulation in the infiltrated areas. However, extravascular infiltration was not detected as long as only a limited tissue volume was investigated. The third reason may involve the relatively low spatial resolutions of PET.

Radiological markers of high sensitivity and specificity are crucial for early diagnosis which leads to initiation of treatment for CNS IVL. The findings of the present case suggest that MET-PET may provide important information on the diagnosis of CNS IVL and on the selection of the optimal site for brain biopsy. Further investigation is necessary to clarify whether positive findings on MET-PET are truly specific and pathognomonic for CNS IVL.

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Statement of Ethics

The Aizawa Hospital Institutional Review Board approved the present study in June 2017 (No. 2017-017). Written permission was obtained prior to MET-PET from the patients' relatives, allowing the use of personal data for clinical research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S. Yomo, T. Hashimoto, K. Oguchi: development of the study concept and protocols. S. Yomo: data collection, manuscript writing. K. Oguchi: assessment of MET-PET. T. Hashimoto: study oversight. All authors critically reviewed and approved the final manuscript.

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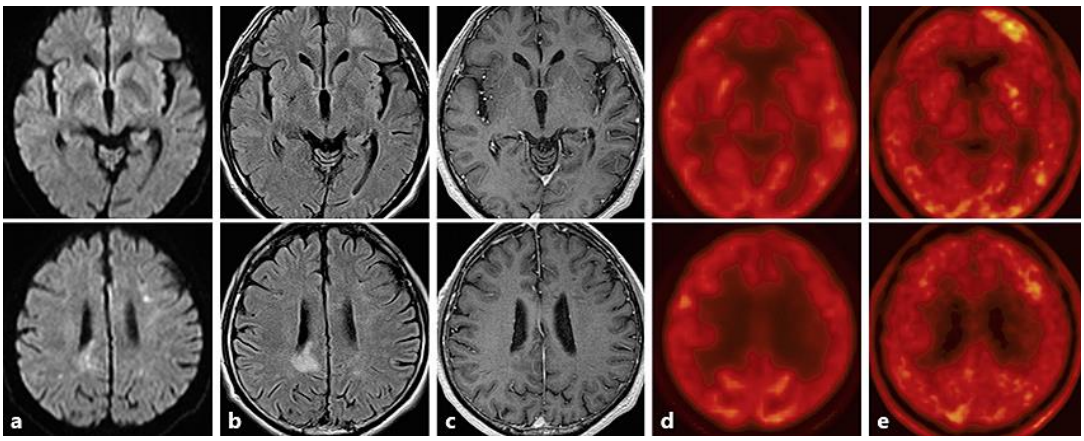

Fig. 1. Brain MRI, FDG-PET, and MET-PET images of a 70-year-old male with CNS IVL. **a** Diffusion-weighted images. **b** FLAIR images. **c** Gadolinium-enhanced T1-weighted images. **d** FDG-PET images. **e** MET-PET images. Diffusion-weighted and FLAIR images showed multiple bihemispheric lesions where gadolinium enhancement was absent. FDG-PET showed slight hypoaccumulation in the frontal cortex (upper panel), while MET-PET showed hyperaccumulation in the left frontal cortex (upper panel), but not in the right posterior cingulate gyrus (lower panel).

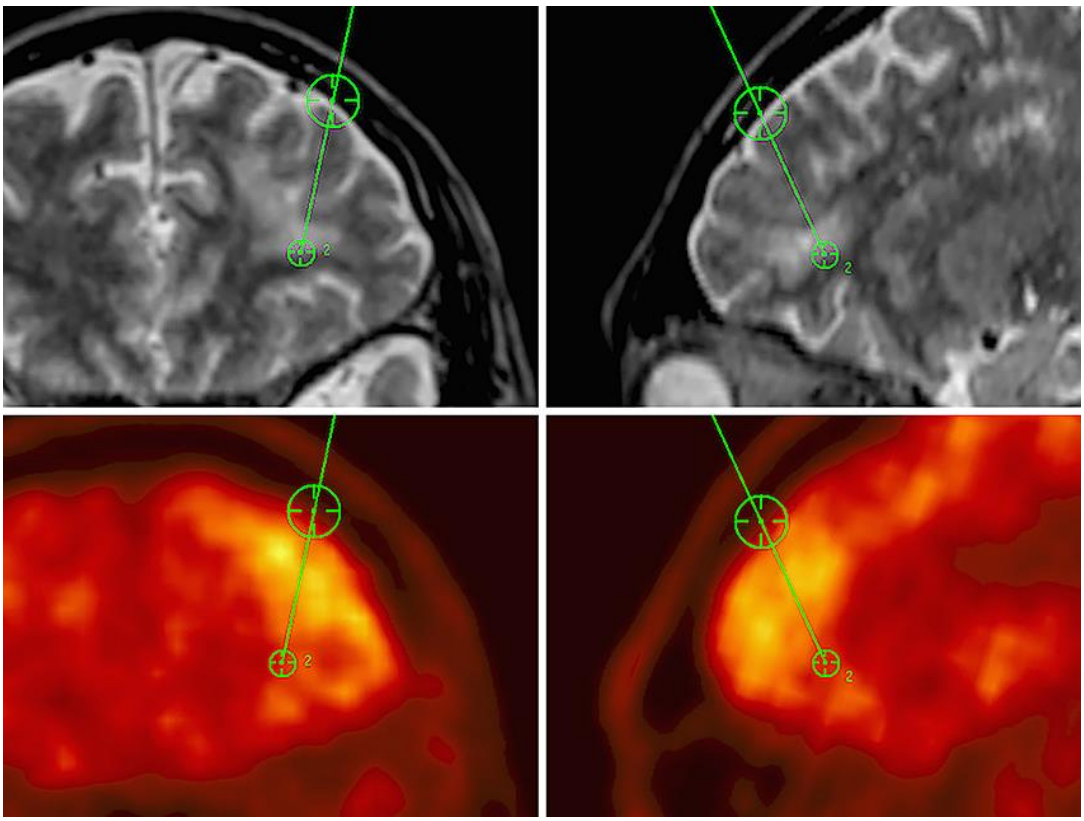

Fig. 2. Stereotactic biopsy planning images. The upper and lower panels show FLAIR and MET-PET images reconstructed into planes parallel to the biopsy trajectory, respectively. Small and large green circles and lines indicate the endpoint, entry point, and trajectory of the biopsy, respectively. Note that the target and trajectory were set on the subcortex through the left frontal cortex corresponding to the area of MET hyperaccumulation.

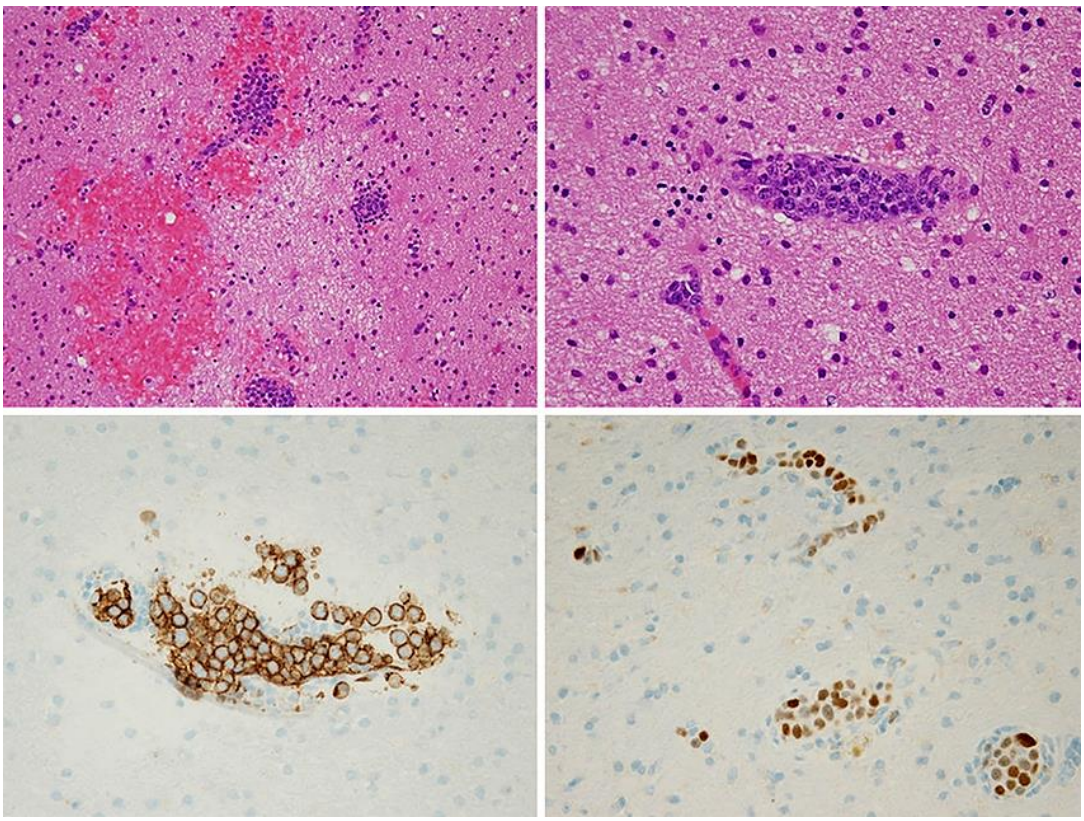

Fig. 3. Microscopic examination. The upper panels show small blood vessels filled with lymphoma cells and perivascular reactive astrocytes. Hematoxylin and eosin staining, original magnification ×20 (left) and ×40 (right). The lower panels show CD20- and MUM1-positive lymphoma cells located exclusively in the lumina of brain vessels with relative sparing of the surrounding tissue. CD20 immunostaining, original magnification ×40 (left); MUM1 immunostaining, original magnification ×40 (right).