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Increased accumulations of *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine related to tumefactive multiple sclerosis

Takao SAGIUCHI,* Hidehiro OKA,* Satoshi UTSUKI,* Kimitoshi SATO,* Ikuo KOBAYASHI,* Yuuji ASANO,** Katsumi ISHII** and Kiyotaka FUJII*

**Department of Neurosurgery, and **Department of Radiology, Kitasato University School of Medicine*

We present a 21-year-old woman with tumefactive multiple sclerosis (MS) that exhibited a rapidly progressive course. There were multiple tumor-mimicking contrast-enhance lesions with surrounding edema and mass effect on magnetic resonance imaging. Both early and delayed brain single photon emission computed tomography (SPECT) with *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine demonstrated increased accumulations of the tracer and a high retention on the lesions. The SPECT findings represent a diagnostic pitfall for distinguishing MS from malignant brain tumors in patients with intracranial tumor-like lesions.

Key words: magnetic resonance imaging, multiple sclerosis, *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine, single photon emission computed tomography

INTRODUCTION

MULTIPLE SCLEROSIS (MS) is characterized by a relapsing and remitting clinical course with periventricular demyelinating lesions on magnetic resonance (MR) imaging.[1] MS with a rapidly progressive course and multiple, large, tumor-like demyelinating lesions on MR imaging is relatively rare.[2–7] The preoperative diagnosis of this type of MS is very difficult because the lesions mimick brain abscess or malignant brain tumors such as glioma, lymphoma, or metastasis and in such cases surgical resection or biopsy is performed. We present a patient with rapidly progressive MS whose multiple tumor-like lesions demonstrated unexpected, increased accumulations of *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine (^{123}I-IMP) on brain single photon emission computed tomography (SPECT).

CASE REPORT

This 21-year-old woman with no relevant medical history suffered from low-grade fever for 2 weeks, gradually worsening headache, and gait disturbance. On admission, blood pressure was 118/80 mm Hg, heart rate was 80/min and regular, and body temperature was 36.6°C. She was confused and neurological examination revealed mild right hemiparesis and right cerebellar ataxia. MR imaging showed multifocal, large, tumor-like lesions with surrounding edema and mass effect in the left occipital lobe, left cerebellum, corpus callosum, and deep white matter. The lesions were hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 1A) with multiple contrast-enhancements (Fig. 1B). On blood laboratory tests, positive findings were limited to a white blood cell count of 11000/μl (normal range 3000–9000/μl) with 82.0% neutrophils and 12.6% lymphocytes. There were no marked abnormalities involving serum C reactive protein, coagulatory and fibrinolytic systems, immunological system, collagen diseases and its associated disease, or tumor markers including lymphoma markers (serum beta 2-microglobulin, serum LDH and soluble IL-2 receptor). Bacterial, fungal, or viral infections including human immunodeficiency virus were negative. Gallium-67-citrate (111 MBq) SPECT showed increased tracer accumulations that corresponded to the contrast-enhanced lesions. Radiologic examinations of extracranial organs did not detect any other tumors. Cerebrospinal fluid was not obtained because of her intracranial hypertension. Immediately after admission an intravenous

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For reprint contact: Takao Sagiuchi, M.D., Department of Neurosurgery, The Kitasato Institute Medical Center Hospital, 6–100, Arai, Kitamoto, Saitama 364–8501, JAPAN.

E-mail: sagiuchi-t@kitasato.or.jp.

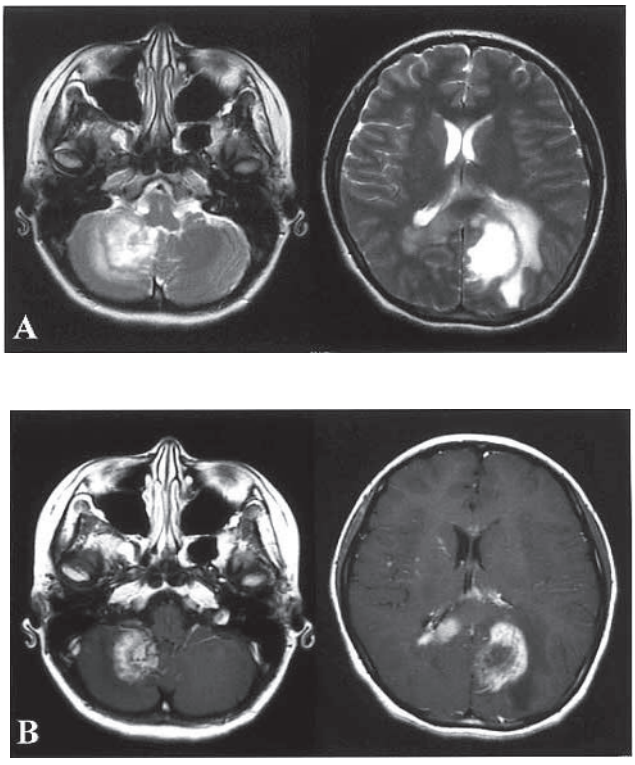

Fig. 1 T2-weighted (A) and contrast-enhanced T1-weighted (B) MR images show a large enhanced lesion with surrounding edema and mass effect in the right cerebellum, a large ring-enhanced lesion with surrounding edema and mass effect with central necrosis in the left occipital lobe, as well as multiple enhancements in the corpus callosum.

administration of betamethasone (20 mg/day) for 2 days was performed, and then the dose was tapered to 4 mg/day during 4 days. Despite high-dose steroid therapy administered twice, there was MR imaging evidence of further enlargement of any lesion and her neurological deficits worsened. The initial clinical and radiological findings were suggestive of acute demyelinating disease or malignant brain neoplasm. On the 14th day after admission, we performed biopsy of the left occipital lesion to decide on the treatment strategy. Intraoperative histological examination of the biopsy specimen revealed perivascular infiltration of polymorphonuclear cells. As these findings were inadequate to distinguish between acute inflammation and primary malignant lymphoma of the central nervous system, quantitative ^{123}I-IMP SPECT was performed immediately after biopsy. Early and delayed SPECT scans were obtained at 15 min and 3 hr after the intravenous administration of ^{123}I-IMP (167 MBq). Each SPECT image showed increased accumulations of the tracer in the right cerebellar- and left occipital lesions (Fig. 2). On early and delayed images, ^{123}I-IMP tumor-to-normal activity (T/N) ratios in the right cerebellar and left occipital lesions were 1.5 and 1.3, and 1.6 and 1.4, respectively, indicating high tracer retention. The ^{123}I-IMP defect and decreased accumulation in the left parieto-occipital region were indicative of postoperative changes. Based on the SPECT findings we suspected malignant lymphoma. However, immunohistopathological examination of the biopsy specimen showed severe demyelination including diffuse axonal injury and infiltration of T-cell lymphocytes and macrophages (Fig. 3). The final diagnosis was multiple sclerosis.

After surgery, demyelinating lesions appeared in the entire spinal cord. She was transferred to an Internal Medicine department for continued steroid- and immunoglobulin therapy. While MR imaging obtained 6 months later showed little contrast-enhancement of the left occipital lesion and corpus callosum, enhancement of the right cerebellum and the cystic formation in the left occipital lobe persisted. She was discharged and continues to receive steroid- and immunoglobulin treatment.

DISCUSSION

On MR studies, atypical MS with acute onset and a rapidly progressive course manifested a large, tumor-like, ring-enhanced lesion with surrounding edema and mass effect. According to Masdeu et al.,[5] on contrast-enhanced MR imaging, patients with tumefactive demyelinating disease show incomplete C-shaped ring-enhancement with no enhancement of the lesion border abutting the white matter. Cha et al.[6] also reported that dynamic contrast-enhanced T2*-weighted MR imaging is a valuable tool for differentiating between tumefactive demyelinating lesions and malignant brain neoplasm. However, atypical MS is often misdiagnosed radiologically as malignant brain neoplasm and patients are subjected to brain biopsy or resection. The results of conventional histopathological examination can also lead to a misdiagnosis of MS as a malignant brain tumor such as high-grade glioma and malignant lymphoma due to the hypercellularity of the lesions, the presence of atypical reactive astrocytes with mitotic figures, perivascular lymphocytic inflammation, necrosis, and edema.[8] For a correct differential diagnosis of MS, immunohistopathological evidence of demyelination is required. In the present case, MR imaging showed left occipital- and right cerebellar lesions that were tumor-like with surrounding edema and mass effect, and multiple contrast-enhanced lesions in the corpus callosum and deep white matter. We suspected acute demyelinating disease based on the patient's poor response to high-dose steroid treatment, our MR imaging and ^{67}Ga SPECT findings, and the absence of elevated tumor markers. However, based on the results of intraoperative histological study and ^{123}I-IMP SPECT images immediately after biopsy, we could not distinguish between MS and malignant lymphoma. Our findings were suggestive of malignant lymphoma rather than MS. ^{123}I-IMP, as a lipophilic agent, easily penetrates the normal blood brain barrier (BBB) and has high extraction efficiency in normal brain

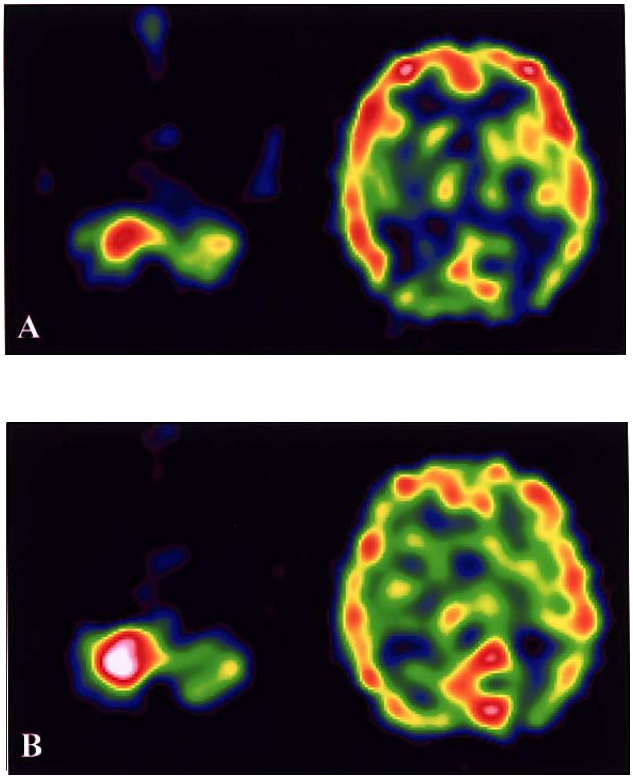

Fig. 2 *N*-Isopropyl-*p*-[^{123}I]-iodoamphetamine (^{123}I-IMP) SPECT immediately after biopsy. A: Early SPECT images show increased accumulations of ^{123}I-IMP in the right cerebellum and left occipital lobe. B: Delayed SPECT images show high retention of the tracer in the right cerebellum and left occipital lobe. The ^{123}I-IMP defect and decreased accumulation in the left parieto-occipital region are indicative of postoperative changes.

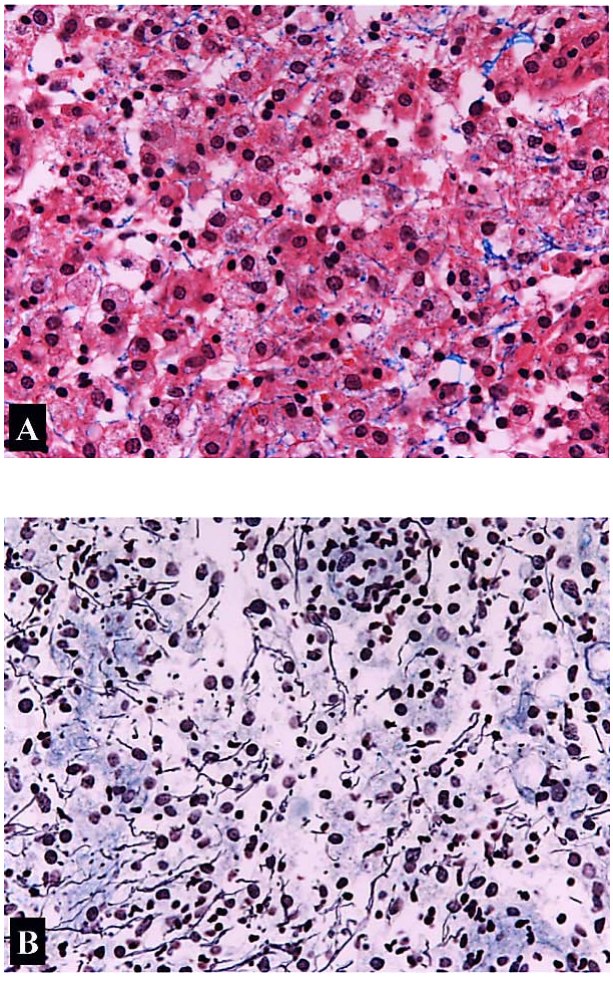

Fig. 3 Luxol fast blue (LFB) + hematoxylin and eosin (HE) (A, × 200) and LFB + Bodian (B, × 200) staining shows an acute demyelinating lesion with axonal injury and with infiltration of T-cell lymphocytes and macrophages.

tissue. Most brain lesions on ^{123}I-IMP SPECT images are visualized as foci of decreased accumulation or defects in ^{123}I-IMP. However, some brain tumors such as malignant lymphoma and -melanoma, glioblastoma, anaplastic astrocytoma, metastatic brain tumor, and meningioma are detected as foci of increased accumulation due to their intravascular retention of the tracer on early ^{123}I-IMP SPECT image.[9] On delayed ^{123}I-IMP SPECT images, malignant lymphoma and -melanoma are detected as foci of increased accumulation due to the existence of amine receptors and amine binding.[9] Therefore, delayed ^{123}I-IMP SPECT is a helpful, non-invasive method for diagnosing malignant lymphoma and -melanoma.[9] However, it is not known whether these tracers accumulate in demyelinating lesions. Our search of the literature detected only one report of ^{123}I-IMP SPECT findings in MS by a Japanese group.[7] In it, Ohkawa et al. documented a patient with acute MS whose MR imaging demonstrated multiple contrast-enhanced lesions that mimicked malignant brain tumor. The lesions manifested a high ^{123}I-IMP uptake on both early and delayed SPECT images. In the present case, early and delayed ^{123}I-IMP SPECT images demonstrated the unexpected, increased accumulation of ^{123}I-IMP in the right cerebellar- and left occipital lesions with mass effect on MR imaging. On early and delayed images, the ^{123}I-IMP T/N ratio was 1.5 and 1.3 in the right cerebellar lesion, and 1.6 and 1.4 in the left occipital lesions, respectively. This is the first report of MS analyzed semi-quantitatively by ^{123}I-IMP SPECT studies. In patients with malignant lymphoma of the central nervous system the early and delayed T/N ratios were 1.03 ± 0.47 and 1.48 ± 0.42, respectively.[9] ^{123}I-IMP T/N ratios in the present case were suggestive of malignant lymphoma. The increased accumulations of ^{123}I-IMP represent a diagnostic pitfall in the differential diagnosis with nuclear medicine studies. On the other hand, the right cerebellar and left occipital lesions as increased accumulations of ^{123}I-IMP manifested persistent contrast-enhancement on MR imaging 6 months after treatment. Although the mechanism of ^{123}I-IMP accumulation related to MS

remains unclear, ^{123}I-IMP SPECT may reflect the extremely high activity of the demyelinating lesions and their resistance to treatment, and may help in assessing the prognosis of individual demyelinating lesions with contrast-enhancement on MR imaging.

CONCLUSION

While ^{123}I-IMP is a useful radiopharmaceutical for the differential diagnosis of malignant brain tumors, the unexpected increased accumulations of ^{123}I-IMP related to MS represents a diagnostic pitfall in the differential diagnosis between MS and malignant brain tumors. Based on these findings we stress that MS should be considered in patients whose tumor-like lesions manifest increased accumulations of ^{123}I-IMP.

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