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Case Study

Secondary Neurolymphomatosis Detected by Whole-Body Diffusion-Weighted Magnetic Resonance Imaging : A Case Report

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Neurolymphomatosis (NL) is a rare clinical entity defined as peripheral nervous system infiltration by lymphoma. The diagnosis is difficult and often elusive. Whole-body diffusion-weighted magnetic resonance imaging (DW MRI) was developed to enhance the detection of vaguely delineated tumors. Here, we describe the case of a 71-year-old male with secondary NL of diffuse large B-cell lymphoma (DLBCL) that was successfully detected by whole-body DW MRI. The patient was diagnosed with DLBCL extending from the ethmoidal sinus to the nasal cavity, orbital cavity, and anterior cranial fossa. Although he was administered R-THP-COP chemotherapy and the tumor remarkably decreased in size, he developed painful paresthesia and weakness in the left upper and bilateral lower extremities during treatment. Because lymphoma cells were detected in his spinal fluid, high-dose methotrexate (MTX) and weekly intrathecal MTX and cytarabine injections were administered. Test results for lymphoma cells in the spinal fluid became negative ; however, the neurological disorders progressed. Whole-body DW MRI was performed as whole-body screening and could localize NL at the left cervical and bilateral lumbar nerve roots. Both cervical spine plain MRI and enhanced computed tomography performed around the same time could not detect the cervical lesion. Our case report suggests that whole-body DW MRI is a useful diagnostic imaging procedure, especially as whole-body screening in facilities where PET/CT is not available. 〔*J Clin Exp Hematop 53(3) : 221-226, 2013*〕

Keywords: neurolymphomatosis, diffusion-weighted magnetic resonance imaging (DW MRI), whole-body magnetic resonance imaging (whole-body MRI), diffuse large B-cell lymphoma, nasal/paranasal lymphoma

INTRODUCTION

Neurolymphomatosis (NL) encompasses infiltration of the peripheral nervous system by neurotropic neoplastic cells in the setting of an unknown or a known hematological malignancy.[1,2] Primary NL is defined as the initial manifestation of the hematological malignancy. On the other hand, secondary NL occurs as relapse or progression of a previously diagnosed lymphoma or leukemia.[1,3] Although the diagnosis is difficult and often elusive, NL has been more frequently diagnosed because of improvements in imaging techniques in recent years. In particular, 2-deoxy-2-[^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) and PET with computed tomography (PET/CT) are useful tools for detecting NL lesions.[1,4-7] However, FDG-PET or PET/CT requires special equipment that can handle radioactive isotopes, and such systems are available in only a limited number of institutions.

Whole-body magnetic resonance imaging (MRI), including diffusion-weighted (DW) MRI, has been studied in the field of oncology with regard to tumor detection, staging, and treatment response monitoring,[8-10] including those for malignant lymphoma.[11-20] A pilot study of patients with diffuse large B-cell lymphoma (DLBCL) revealed that whole-body DW MRI findings were consistent with PET/CT findings in 94% of node regions, yielding sensitivity and specificity of 90% and 94%, respectively.[13]

Here, we describe a case of secondary NL of DLBCL that was successfully diagnosed by whole-body DW MRI.

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CASE REPORT

A 71-year-old Japanese male with no significant past history except for lumbar canal stenosis developed right eye

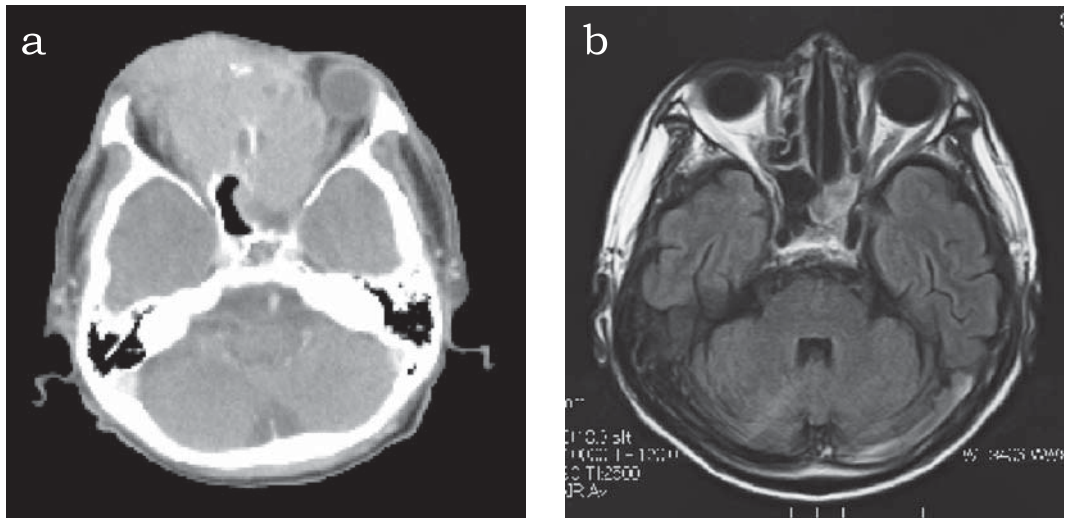

Fig. 1. Contrast-enhanced computed tomography revealed a tumor extending from the ethmoidal sinus to the nasal cavity, the right orbital cavity, and the anterior cranial fossa (*1a*). Brain magnetic resonance imaging after three courses of R-THP-COP chemotherapy revealed that the tumor in the ethmoidal sinus remarkably decreased in size. Definite infiltrated regions were not detected in the cranial region *(1b)*.

swelling and decreased vision in June 2009. Contrast-enhanced CT revealed a tumor extending from the ethmoidal sinus to the nasal cavity, orbital cavity, and anterior cranial fossa (Fig. 1a). Lymphadenopathy was present in the right parotid gland and bilateral cervical region, with no other lesions in the chest, abdomen, and bone marrow. A biopsy of the tumor in the nasal cavity revealed DLBCL. We diagnosed the patient with DLBCL at stage IIA. Because of progression of visual disorder and ophthalmalgia, immediate chemotherapy was needed and PET/CT, which was not available in our hospital, could not be performed.

R-THP-COP chemotherapy (rituximab, 375 mg/m^2, day 1 ; pirarubicin, 30 mg/m^2, day 2 ; vincristine, 1.4 mg/m^2, day 2 ; cyclophosphamide, 750 mg/m^2, day 2 ; prednisolone, 80 mg/body, day 1-5, every 3 weeks) was initiated, following which the tumor remarkably decreased in size. Definite infiltration was not detected in the cranial region (Fig. 1b). The patient refused a central nervous system (CNS) prophylaxis procedure and examination of his cerebrospinal fluid (CSF) because of a long history of recurrent severe back pain caused by spinal canal stenosis. After three courses of R-THP-COP chemotherapy, he developed back pain and bilateral painful paresthesia in the lower extremities. Brain MRI ruled out regrowth of the tumor in the ethmoidal sinus. Lumbar spine plain MRI revealed no abnormal findings except for spinal canal stenosis and laterality of iliopsoas muscle was not pointed out. A nonsteroidal anti-inflammatory drug was administered, but back pain and paresthesias were exacerbated. Subsequently, left upper extremity weakness and painful paresthesias developed, and he was admitted to our hospital in October 2009.

Laboratory tests revealed that blood cell count, serum lactate dehydrogenase, and soluble interleukin-2 receptor levels were within the normal range, but CSF examination revealed remarkable pleocytosis (1,274/mm^3) that mostly consisted of lymphoma cells. The patient was administered high-dose methotrexate (MTX ; 2 g/m^2) combined with weekly intrathecal MTX and cytarabine injections, following which test results for lymphoma cells in the CSF became negative. However, painful paresthesia and weakness in the left upper and bilateral lower extremities improved only temporarily. Additional cervical spine plain MRI and re-examination by chest and abdominal plain CT in November 2009 detected no new lesions or regrowth of lymphoma. NL was strongly suspected but other causes of neuropathy could not be ruled out, such as infectious, paraneoplastic or therapy-related disorders of root and nerve, Guillain-Barre syndrome, or chronic inflammatory demyelinating polyneuropathy. In terms of PET/CT, it was difficult to transfer the patient to another facility to undergo the test because of his poor general condition. We performed whole-body DW MRI as whole-body screening.

A 1.5-T system (EXCELART Vantage XGV ; Toshiba Medical Systems Corporation, Japan) was used to perform whole-body DW MRI. A 3-element phase-array surface coil for signal reception was used to acquire axial DW images of the head/neck, chest, and abdomen under free breathing conditions. Applied sequence parameters for DWI were as follows : single-shot spin-echo echo-planar mode with spectrally selective fat saturation ; TR/TE/IR, 117, 700/80/150 ms ; slice thickness/gap, 9/-1 mm ; number of slices, 42 ; field of view, 400 × 480 mm^2 ; acquisition matrix, 128 ×

112 ; motion probing gradients in six orthogonal axes ; *b* values, 1,000 sec/mm^2 ; number of acquisitions, 3 ; parallel imaging (Sensitivity Encoding) factor, 1.8 ; acquired voxel size, 3.57 × 3.57 × 9 mm^3 ; and scan time, 5 min and 47 sec.

Whole-body DW MRI detected the tumors in the ethmoidal sinus (Fig. 2a) and the bilateral iliopsoas muscles (Fig. 2b, 2c), as well as lesions in the left C5 nerve root (Fig. 2g, 2h, 2i). After the whole-body DW MRI was performed, contrast-enhanced CT was performed to confirm the detection. It revealed that there were enhanced tumors in the ethmoidal sinus (Fig. 2d) and the bilateral iliopsoas muscles (Fig. 2e, 2f). However, the lesions in the left C5 nerve root were not detected.

Immediately after the study, the patient developed dysphagia and right ptosis. Because of a poor general status caused by aspiration pneumonia and a urinary tract infection, additional chemotherapy could not be administered. Palliative therapy was initiated, and the patient died from disease progression in December 2009.

DISCUSSION

DW MRI noninvasively probes the random microscopic motion of water molecules in the body.[21] Tumors are frequently more cellular than the tissue from which they originate ; therefore, they appear to exhibit relatively high signal intensity (restriction of water diffusion). The localization of malignant lymphoma is usually well visualized on whole-body DW MRI because high cellularity and a high nuclear-to-cytoplasm ratio are suitable for DW MRI.[12] In diagnosing NL, enhanced MRI is useful by revealing enlargement and enhancement of the affected nerve,[22,23] although it may not always provide optimal visualization of lymphomatous involvement.[2,5,7] In addition, it is difficult for enhanced MRI to evaluate the whole range of the spinal cord at once. On the other hand, whole-body DW MRI, which reflects tissue structure and cellularity, could diagnose NL without anatomical abnormalities in lesions of lymphomatous involvement. The total scan time of the whole body was approximately 35 to 40 min in our hospital and injection of contrast agents is unnecessary for DW MRI. Recently, there were some studies that compared whole-body DW MRI and PET/CT for staging of malignant lymphoma. Stéphane *et al*. described in a study on 23 patients with lymphoma that whole-body DW MRI and PET/CT results were congruent in 97% of nodal lesions and in 99% of extranodal lesions.[17] Gu *et al*. reported that the diagnosis sensitivity of whole-body DW MRI compared with PET/CT as a standard of reference was 97% for the diagnosis of 130 lesions in 17 patients with malignant lymphoma.[18] Abdulqadhr *et al*. described in a study of 31 patients with lymphoma that Ann Arbor staging was the same for whole-body DW MRI and PET/CT in 28 (90.3%) patients and different in three (9.7%), who were patients with indolent small lymphocytic lymphoma/chronic lymphocytic leukemia lymphoma.[19] van Ufford *et al*. reported in a study on 22 patients with lymphoma that the staging according to whole-body DW MRI findings was concordant with that of PET/CT findings in 77% (17/22) of patients. Understaging and overstaging relative to the findings with PET/CT occurred in 0% (0/22) and 23% (5/22) of cases. Four of 5 overstaging patients were diagnosed with indolent lymphoma.[20] For the staging of aggressive lymphoma, the diagnostic accuracy of DW MRI appears to be equal to that of PET/CT. However, these studies all included relatively small numbers of patients and a larger prospective study is necessary to confirm the usefulness of whole-body DW MRI for staging of lymphoma.

Unfortunately, in our case, histological confirmation of the lesion at left cervical root could not be performed and a report described that normal brachial plexus can be depicted by DW MRI.[24] However, we confirmed the lymphoma cells in CSF and DW MRI detected abnormal signals in only the left cervical root, not bilaterally, which could demonstrate the left upper extremity weakness and painful paresthesias. Painful involvement of roots is one of the most common clinical presentations of NL.[2] These findings met the inclusion criteria of secondary NL.[1,2] Patients with DLBCL involving nasal/paranasal sinus region have significantly higher incidence of secondary CNS disease and CNS prophylaxis is recommended for these patients.[25,26] Because CNS prophylaxis was not performed in our case, there might have been residual lymphoma cells in cervical roots as well as CSF and secondary NL might have been presented. Tissue diagnosis of NL is often difficult ; diagnosis of NL was not established until autopsy in 45% of patients in a previous study.[2] Tissue diagnosis of NL is strongly recommended whenever feasible, but the need to initiate treatment in patients in whom tissue diagnosis fails is also recognized.

As therapies for secondary CNS disease, our patient received high-dose MTX chemotherapy and intrathecal injections, following which test results for lymphoma cells in the CSF became negative. However, his neurological symptoms did not improve. In patients with NL, the use of intrathecal chemotherapy alone cannot eliminate involvement in all the roots, nerves, extradural nerve roots, plexuses, and peripheral nerves.[2] MTX doses up to 8 g/m^2 provide therapeutic concentrations to the brain,[27] spinal fluid, and, presumably, lymphoma in intradural and extradural root and nerve sites.[2] Although there are some case reports describing successful treatment by 8 g/m^2 MTX chemotherapy with or without other systemic chemotherapy,[2,5] various doses of MTX were administered according to patient age and complications because high-dose MTX chemotherapy has severe renal toxicity.[1,7] In our case, MTX chemotherapy at doses up to 2 g/m^2 may have been sufficient to eliminate the CSF lymphoma cells but insufficient to eliminate the lymphoma cells in the left cervical extradural nerve roots. The tumor in left

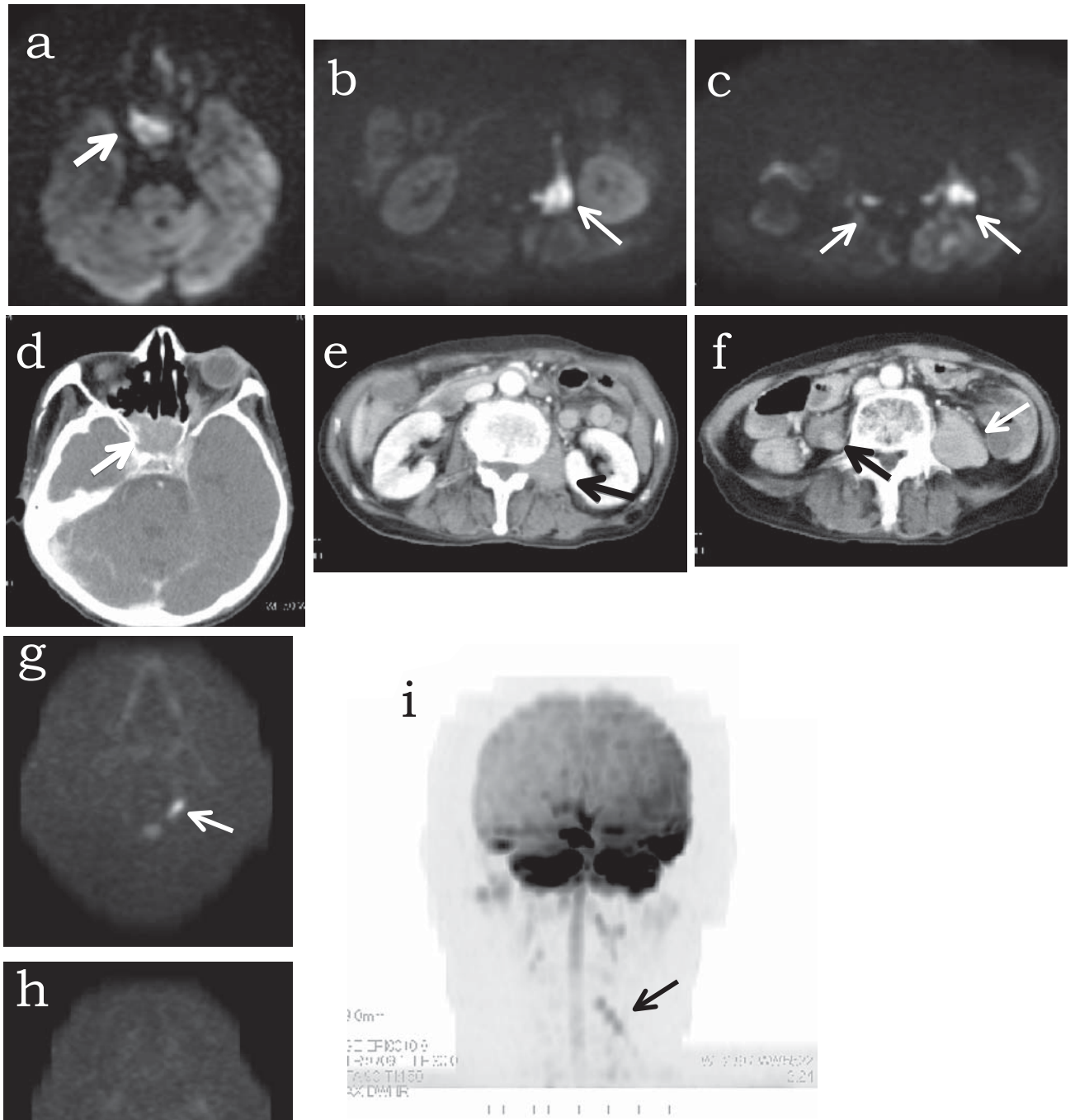

Fig. 2. Whole-body diffusion-weighted magnetic resonance imaging (DW MRI) detected the tumors in the ethmoidal sinus (*2a*), the bilateral iliopsoas muscles (*2b*, *2c*), and lesions in the left C5 nerve root (*2g*, *2h*, *2i*). Contrast-enhanced computed tomography after the whole-body DW MRI revealed that there were enhanced tumors in the ethmoidal sinus (*2d*) and the bilateral iliopsoas muscles (*2e*, *2f*). However, the lesions in left C5 nerve root were not detected.

iliopsoas muscle seemed to extend to the right L2 nerve root (Fig. 2b, 2e). It is suggested that the residual lymphoma cells in extradural lumbar roots might rapidly extend to the iliopsoas muscles. Our case suggests that high-dose MTX as central and peripheral nervous system chemoprophylaxis is needed for patients with a high risk of secondary CNS disease, even if examination of CSF and intrathecal chemotherapy cannot performed, and that it is necessary to include NL in the differential diagnosis of neurological disorder in these patients, and PET/CT or whole-body DW MRI, if PET/CT is not immediately available, should be performed in addition to examination of the CSF and brain MRI.

In conclusion, we experienced a case with secondary NL of DLBCL that presented during chemotherapy and was successfully detected by whole-body DW MRI. It could not be detected by both cervical plain MRI and contrast-enhanced CT, which were performed around the same time. This case report suggests that whole-body DW MRI is superior to plain MRI in the detection of NL and is a useful diagnostic imaging procedure, especially as whole-body screening in facilities where PET/CT is not available.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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