

Multifocal Inflammatory Leukoencephalopathy: Use of Thallium-201 SPECT and Proton MRS

In a patient receiving 5-fluorouracil and levamisole, neurologic deficits suggest the cerebral demyelinating syndrome as a differential diagnosis. The authors report a patient diagnosed as multifocal inflammatory leukoencephalopathy for which thallium-201 (^{201}Tl) single photon emission computed tomography (SPECT) and proton magnetic resonance spectroscopy (MRS) were employed as noninvasive diagnostic tools. ^{201}Tl SPECT study was negative and proton MRS showed an increase of choline and lactate and well preserved *N*-acetylaspartate. These findings support histopathologic findings of multifocal inflammatory leukoencephalopathy revealing demyelination with relative axonal sparing in the patient.

Key Words : *Leukoencephalopathy; Fluorouracil; Levamisole; Magnetic Resonance Spectroscopy; Tomography, Emission Computed, Singl-Photon*

**Yang Ha Hwang, Chung Kyu Suh,
Sung Pa Park**

Department of Neurology, School of Medicine,
Kyungpook National University, Daegu, Korea

Received : 29 July 2002

Accepted : 11 September 2002

Address for correspondence

Sung Pa Park, M.D.

Department of Neurology, School of Medicine,
Kyungpook National University, 50 Samduk 2Ga
Joong-gu, Daegu 700-721, Korea

Tel : +82.53-420-5760, Fax : +82.53-422-4265

E-mail : sppark@knu.ac.kr

INTRODUCTION

Multifocal inflammatory leukoencephalopathy (MIL) is a rare syndrome associated with 5-fluorouracil (5-FU) and levamisole chemotherapy (1-6). The radiographic and clinical features of this syndrome often pose difficulties in distinguishing it from other diseases, especially multiple brain metastases. We herein describe a patient with MIL related to oral tegafur (derivative of 5-FU) and levamisole therapy using thallium-201 (^{201}Tl) single photon emission computed tomography (SPECT) and proton magnetic resonance spectroscopy (MRS) as adjunctive noninvasive tools in the diagnosis of this reversible syndrome.

CASE REPORT

A 45-yr-old man was admitted to our department with a gradual onset of right hemiparesis, left facial and arm paresthesias, and hiccups. Five months before admission, he had undergone primary resection of adenocarcinoma of the rectum. Two months after the operation, he received adjuvant chemotherapy with tegafur ([1-(2-tetrahydrofuryl)-5-FU], 600 mg/day orally) and levamisole (100 mg/day orally for three days, each week) for moderately differentiated stage II adenocarcinoma. One month before admission, he developed paresthesia in the left face and arm, and complained of intermittent hiccups. One week later, he experienced progressive weakness of right extremities and gait disturbance. On admission, he was alert with intact cognitive function. Neurologic

examination showed decreased left facial and arm sensation, mild right hemiparesis, moderately increased deep tendon reflexes, and clumsiness of right side on gait. He was afebrile throughout the illness.

Brain MRI revealed multiple, ring- or nodular-enhancing white matter lesions, scattered throughout the cerebral hemispheres and two separate non-enhancing brainstem lesions involving the left middle cerebellar peduncle and dorsolateral medulla oblongata (Fig. 1). Cerebrospinal fluid (CSF) examination showed a normal opening pressure, pleocytosis (22 cells/ μL , 90% of lymphocytes), normal glucose, and increased protein; cultures for bacterial, fungal, and acid-fast bacilli, and cytologic findings were negative; ELISA test for parasites and PCR test for viruses were all negative. Other general laboratory tests revealed no abnormalities.

On the fourth day of admission, proton MRS (Siemens Vision Plus 1.5T, PRESS 2D with single voxel) was performed, which revealed high choline (Cho) and lactate with relative preservation of *N*-acetylaspartate (NAA) (Fig. 2). On the 10th day, brain ^{201}Tl SPECT showed no abnormal uptake. A stereotactic brain biopsy targeting the ring-enhancing lesion in the left frontal area was done on the 14th day.

Histopathology revealed demyelinating lesions in white matter with relative axonal sparing; perivascular lymphocytic cuffing, macrophage infiltration, and scattered hyperplastic astrocytes were noted.

With discontinuation of tegafur and levamisole, he began to receive corticosteroid therapy. Two weeks after discharge, his neurologic condition improved markedly, as evidenced by improved extremity weakness and paresthesia. Repeated brain

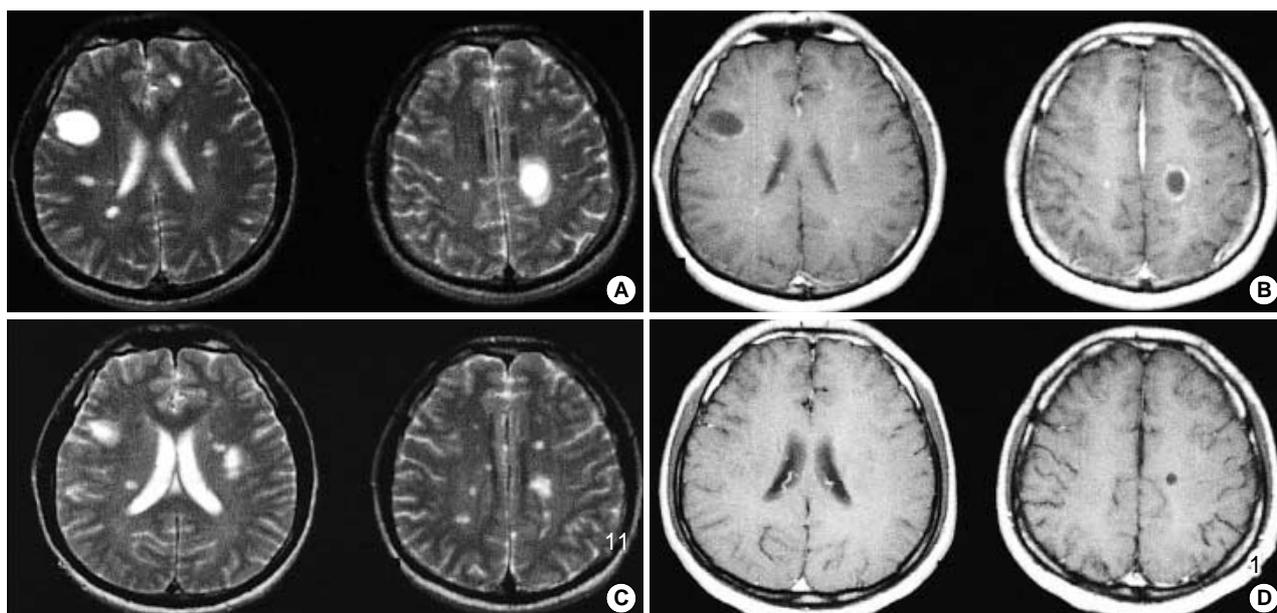


Fig. 1. Brain MRI with gadolinium enhancement. (A, B) T2-weighted images and T1-weighted images after gadolinium administration at the time of presentation. (C, D) T2-weighted images and T1-weighted images after gadolinium administration at follow-up after corticosteroid therapy, which show markedly resolving subcortical enhancing lesions.

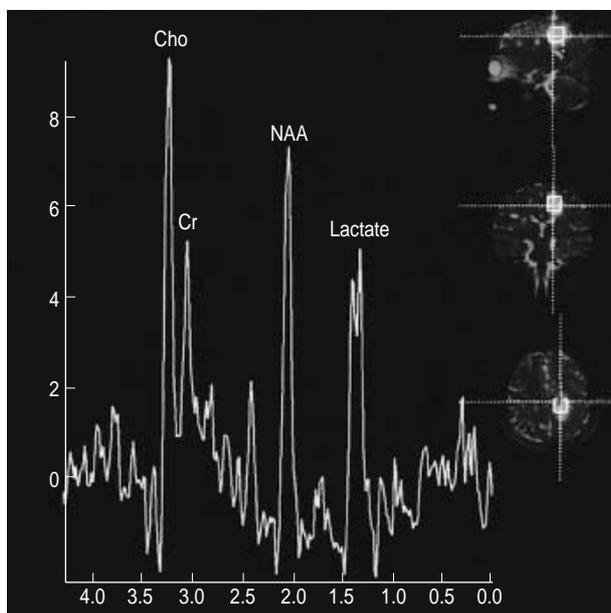


Fig. 2. Proton MRS shows increased choline and lactate with relatively normal *N*-acetylaspartate consistent with demyelination.

MRI performed two months after discontinuation of this regimen revealed decreased, but persistent, multifocal cerebral and brainstem T2 hyperintensities; however, none of these lesions were enhanced.

DISCUSSION

There are several clinical reports of MIL developed in patients

treated with 5-FU and levamisole or levamisole alone (1-6). The clinical features of this syndrome are subacute progressive neurologic symptoms and signs including confusion, behavioral change, memory impairment, dysarthria, paresthesia, hemiparesis, ataxia, and diplopia. All developed within five months of initiation of therapy (1-6). Brain MRI revealed multiple enhancing white matter lesions with predilection for the periventricular areas (1-6). CSF studies revealed mild pleocytosis, increased protein, and sometimes the presence of an oligoclonal band, increased IgG index, or elevated TNF- α level (1, 2). All patients improved once 5-FU and levamisole were discontinued (1-6). A beneficial response to short-term treatment with corticosteroids was also observed. Repeated imaging studies demonstrated loss of lesion enhancement and decreased size of lesions (3-5). Stereotactic brain biopsy revealed an inflammatory demyelinating lesion with relative axonal sparing (1-3, 6).

Both levamisole and 5-FU have been implicated in the etiology of this syndrome. However, the pathogenesis of this syndrome has not been clarified. In normal mice, levamisole and 5-FU are not directly toxic to myelin (7). When these agents are administered to mice infected with a demyelination-inducing virus, however, demyelination and inflammation are augmented and accelerated (7). Thus, treatment with levamisole and 5-FU may enhance a pathologic immune response toward a persistent antigen capable of producing demyelinating disease in a susceptible host (7).

Among 1,030 patients treated with levamisole alone or levamisole and 5-FU as a surgical adjuvant therapy for colon cancer, neurologic symptoms or signs developed in 3.1% of all cases during treatment and in 4.5% of patients treated with

levamisole and 5-FU (2). However, there are few case reports on MIL related to this regimen (1-6). With above findings, it may be assumed that physicians might have misdiagnosed the disease as other diseases, especially multiple brain metastases. There was one patient with MIL who initially was misdiagnosed as multiple brain metastases and received radiotherapy for two weeks (1). Thus, it is important to differentiate this benign reversible demyelinating syndrome from other diseases.

The differential diagnosis of patients receiving 5-FU and levamisole presenting with multiple white matter lesions includes metastatic intracranial colon carcinoma, brain abscesses, multicentric glioma, primary central nervous system lymphoma, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML). In our patient, immunocompetent state, negative CSF ELISA test for toxoplasmosis, and no viral inclusions in brain biopsy make the diagnosis of toxoplasmosis or PML unlikely. The discrimination between MIL and multiple brain metastases is difficult problem in clinical and laboratory backgrounds.

²⁰¹Tl SPECT is a noninvasive method which may help to differentiate intracranial tumors from other non-neoplastic diseases (8). Uptake of ²⁰¹Tl into tumor cells may be related to multiple factors, including regional blood flow, blood-brain barrier permeability, and cellular uptake. The sensitivity of ²⁰¹Tl SPECT for supratentorial tumors in general was 71.7% and specificity was 80.9% in one study (8). In their subgroup of 14 patients with brain metastases, only one patient with pontine metastasis was negative on the scan (8). One patient who showed multiple enhancing white matter lesions in MRI and in whom brain metastasis was suspicious was diagnosed as MIL aided with negative ²⁰¹Tl SPECT and active demyelination revealed by histopathologic examination (3). ²⁰¹Tl SPECT was also negative in our patient. Based on this previous case and our experience, we could speculate that negative ²⁰¹Tl SPECT may be helpful in the diagnosis of MIL in patients receiving 5-FU and levamisole.

Accurate histologic diagnosis is most important, especially when atypical pattern of malignancy is suspected. It may change the treatment plan or clinical outcome in such cases when supported by stereotactic or open brain biopsy. However, these procedures have significant limitations or risks, such as inadequate specimens, lesions of high surgical risks, or surgical or anesthetic complications. Proton MRS provides more information in tissue characterization and may be helpful in differential diagnosis of intracranial mass lesions. In 15 patients with suspicious primary brain tumors, proton MRS was used to compare histopathology with MRS interpretation (9). MRS accurately predicted the pathological nature and clinical outcome of lesions in 15/16 (96%) situations, and influenced clinical decision making in 12 cases, and altered surgery planning in seven patients (9). In three young patients with suspicious multiple sclerosis, MRS-detected decrease of NAA was correlated with a relative decrease of axonal density in immuno-

pathology of corresponding biopsy specimens (10). Concomitant increases of Cho and myo-inositol corresponded to glial proliferation, and elevated lactate levels were associated with inflammation (10). In our patient, proton MRS revealed increased Cho and lactate, which reflected demyelination and inflammation processes with macrophage activation considering histopathologic findings. The NAA, as an indicator of neuroaxonal integrity, was not decreased, which explains excellent clinical recovery after discontinuation of the regimen and well-preserved axons on histopathology.

As far as we know, our patient is the first case of MIL in which MRS findings consistent with histopathology of MIL were demonstrated. We performed stereotactic brain biopsy for the confirmatory diagnosis; however, the results of MRS and SPECT in our patient may offer valuable information on the management of MIL in the future. In colorectal cancer patients receiving 5-FU and levamisole or levamisole alone develop focal neurologic deficit, if brain MR imaging or CT shows multifocal enhancing lesions, we recommend proton MRS, brain ²⁰¹Tl SPECT, or both as noninvasive diagnostic tools to exclude brain metastasis before stereotactic brain biopsy.

REFERENCES

1. Israel ZH, Lossos A, Barak V, Soffer D, Siegal T. *Multifocal demyelinating leukoencephalopathy associated with 5-fluorouracil and levamisole. Acta Oncol* 2000; 39: 117-20.
2. Hook CC, Kimmel DW, Kvols LK, Scheithauer BW, Forsyth PA, Rubin J, Moertel CG, Rodriguez M. *Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. Ann Neurol* 1992; 31: 262-7.
3. Savarese DM, Gordon J, Smith TW, Litofsky NS, Licho R, Ragland R, Recht L. *Cerebral demyelination syndrome in a patient treated with 5-fluorouracil and levamisole: the use of thallium SPECT imaging to assist in noninvasive diagnosis? A case report. Cancer* 1996; 77: 387-94.
4. Kimmel DW, Wijdicks EF, Rodriguez M. *Multifocal inflammatory leukoencephalopathy associated with levamisole therapy. Neurology* 1995; 45: 374-6.
5. Chen TC, Hinton DR, Leichman L, Atkinson RD, Apuzzo ML, Couldwell WT. *Multifocal inflammatory leukoencephalopathy associated with levamisole and 5-fluorouracil: case report. Neurosurgery* 1994; 35: 1138-43.
6. Fassas AB, Gattani AM, Morgello S. *Cerebral demyelination with 5-fluorouracil and levamisole. Cancer Invest* 1994; 12: 379-83.
7. Lucchinetti CF, Kimmel DW, Pavelko K, Rodriguez M. *5-Fluorouracil and levamisole exacerbate demyelination in susceptible mice infected with Theiler's virus. Exp Neurol* 1997; 147: 123-9.
8. Dierckx RA, Martin JJ, Dobbeleir A, Crols R, Neetens I, De Deyn PP. *Sensitivity and specificity of thallium-201 single photon emission tomography in the functional detection and differential diagnosis of brain tumours. Eur J Nucl Med* 1994; 21: 621-33.
9. Lin A, Bluml S, Mamelak AN. *Efficacy of proton magnetic resonance*

spectroscopy in clinical decision making for patients with suspected malignant brain tumors. J Neurooncol 1999; 45: 69-81.

10. Bitsch A, Bruhn H, Vougioukas V, Stringaris A, Lassmann H, Frahm

J, Bruck W. *Inflammatory CNS demyelination: histopathologic correlation with in vivo quantitative proton MR spectroscopy. Am J Neuroradiol 1999; 20: 1619-27.*