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

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BACKGROUND. The use of 5-fluorouracil (5-FU) and levamisole in patients with Stage III adenocarcinoma of the colon has now become standard. There have been several reports of a multifocal cerebral demyelination syndrome following 5-FU and levamisole administration.

METHODS. We describe a patient who developed focal neurologic symptoms while being treated with levamisole and 5-FU in whom the diagnosis of central nervous system (CNS) metastases was considered.

RESULTS. A magnetic resonance imaging (MRI) scan showed a diffuse, multifocal white matter process. Diagnostic evaluation did not support a diagnosis of CNS metastasis. ^{201}Thallium chloride single photon emission computed tomography (SPECT) study was cold. A stereotactic brain biopsy disclosed demyelination but not tumor. The patient had complete functional resolution of symptoms with 1 month of dexamethasone therapy, although follow-up MRI scans have shown persistent abnormality on T2-weighted images.

CONCLUSIONS. In patients receiving 5-FU and levamisole who develop focal neurologic symptoms with an abnormal MRI scan, the diagnosis of CNS metastasis should not be made without a thorough diagnostic evaluation. We suggest the use of ^{201}thallium chloride SPECT imaging to support the diagnosis of multifocal leukoencephalopathy related to 5-FU and levamisole. In atypical cases, a stereotactic brain biopsy may be required for confirmation. ***Cancer* 1996; 77:387–94.**
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5-Fluorouracil (5-FU) and levamisole have been shown to decrease the risk of clinical recurrence and to increase survival in patients with Stage III adenocarcinoma of the colon, in whom adjuvant chemotherapy has now become standard.[1,2] In general, this treatment has been well tolerated; however, there are now several clinical reports of cerebral demyelination associated with 5-FU and levamisole administration. This appears to be a rare toxicity, with only 10 cases currently reported in the literature.[3–7] The clinical picture may be confused with multiple brain metastases. We describe an additional patient who developed cerebral demyelination following 5-FU and levamisole treatment, and we report the use of radionuclide single photon emission computed tomography (SPECT) brain scanning with thallium-201 (^{201}Tl) as an additional noninvasive study supporting the nonmetastatic nature of this syndrome.

CASE REPORT

A 68-year-old white woman was admitted to the hospital with gradual onset of left facial weakness, slurred speech, ataxia, and left arm and

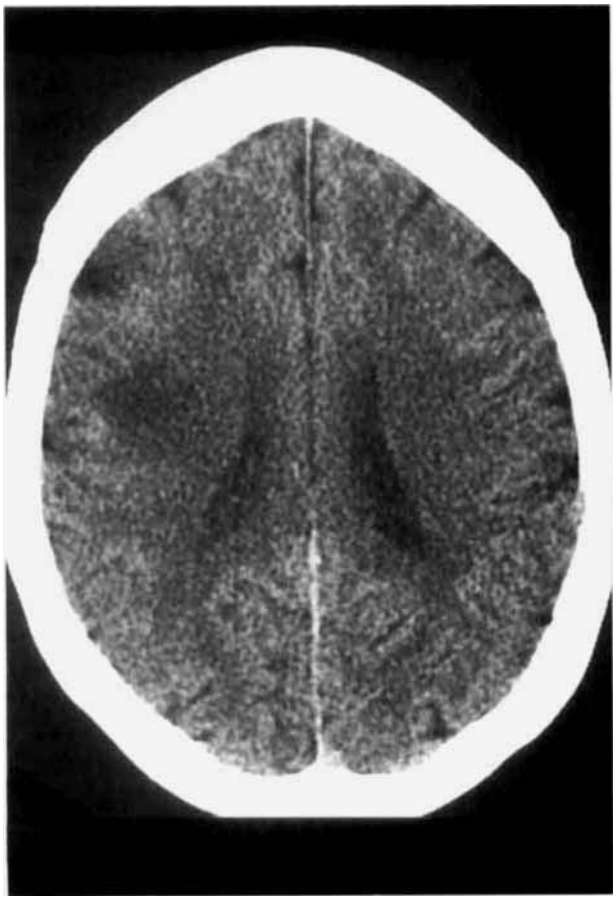

FIGURE 1. Contrast enhanced CT. A focal patch of hypodensity is seen within the corona radiata on the right. There is questionable faint enhancement at the lateral aspect of the lesion and fullness of the brain parenchyma at this site.

leg weakness. She had received 8 weeks of adjuvant 5-FU/levamisole treatment for a moderately differentiated Stage III adenocarcinoma of the sigmoid colon. Prior to sigmoid resection, the carcinoembryonic antigen (CEA) level was 25.5 ng/ml (normal, less than 3.0 ng/ml). Postoperatively, the CEA level had declined to 1.7 ng/ml.

Ten days prior to admission, she developed a left facial nerve palsy. Computed tomography (CT) scan of the brain with intravenous contrast showed only a vague, nonspecific focus of low density in the right corona radiata/centrum semiovale, without evidence of clear-cut abnormal enhancement; there was a suggestion of some slight ventricular effacement (Fig. 1). This abnormality was thought to be of a possible ischemic nature, but an unusual metastasis could not be excluded. Four days later, symptoms improved without specific therapy, and further 5-FU was administered. Levamisole was held due to nausea and anorexia. Four days after receiving additional 5-FU, the patient presented with new focal neurologic deficits, as noted above, and was admitted to the hospital. At the time of admission, the patient had received a total 5-FU dose of 8,900 mg and a total levamisole dose of 1,350 mg. She had been receiving no other medications. A magnetic resonance imaging (MRI) scan of the brain without and with intravenous gadolinium contrast revealed multiple, bilateral infratentorial and supratentorial enhancing lesions associated with only quite mild right lateral ventricular effacement (Fig. 2A). The postgadolinium T1 axial image at the level of the corona radiata revealed irregular ring-type enhancement at the right cerebral white matter oriented toward the gray-white junction (Fig. 2B). Given the central T2 hyperintensity and the paucity of mass effect relative to the size of the lesion, the MRI features were felt to be somewhat atypical for a brain metastasis. Even so, a presumptive diagnosis of central nervous system (CNS) metastasis was made. The patient was begun on dexamethasone 4 mg every 6 hours intravenously with slight improvement in the left arm and leg weakness. However, the CEA level was reported to be 1.3 ng/ml, and CT scan of the abdomen and pelvis revealed no evidence of recurrent disease.

On the fourth hospital day, a lumbar puncture was performed. Cerebrospinal fluid protein was 42 mg/dl (normal, 20–40 mg/dl), and no malignant cells were noted on cytologic examination. A radionuclide SPECT scan of the brain with ^{201}Tl revealed no uptake (Fig. 3).

On the seventh hospital day, the patient underwent CT-guided stereotactic brain biopsy with delayed intravenous contrast, targeting the center of the homogeneously enhancing lesion in the right centrum semiovale. Histopathologic examination revealed a well circumscribed area of active demyelination with relative axonal sparing (Fig. 4). Reactive gliosis, focal perivascular mononuclear cell inflammation, and macrophage infiltration were noted within the demyelinating lesion. No malignant cells, viral inclusions, or vasculitis were noted. The patient was treated with continued dexamethasone with a slow taper over 1 month, and her neurologic symptoms gradually resolved. Repeat brain MRI scans performed 1 and 2 months after discontinuation of steroids showed decreased, but persistent, multifocal cerebral and cerebellar T2 hyperintensity; however, the previously noted irregular ring enhancement at the right side of the corona radiata had resolved (Fig. 5).

DISCUSSION

Up to 10 cases of a multifocal demyelinating process occurring in patients with colorectal cancer treated with adjuvant 5-FU and levamisole have been reported[3–7] (Table 1). In addition to the patients referenced in Table 1, Leichman et al.[7] reported, in abstract form, three patients from separate centers who developed personality changes, seizures, disorientation or focal neurologic signs

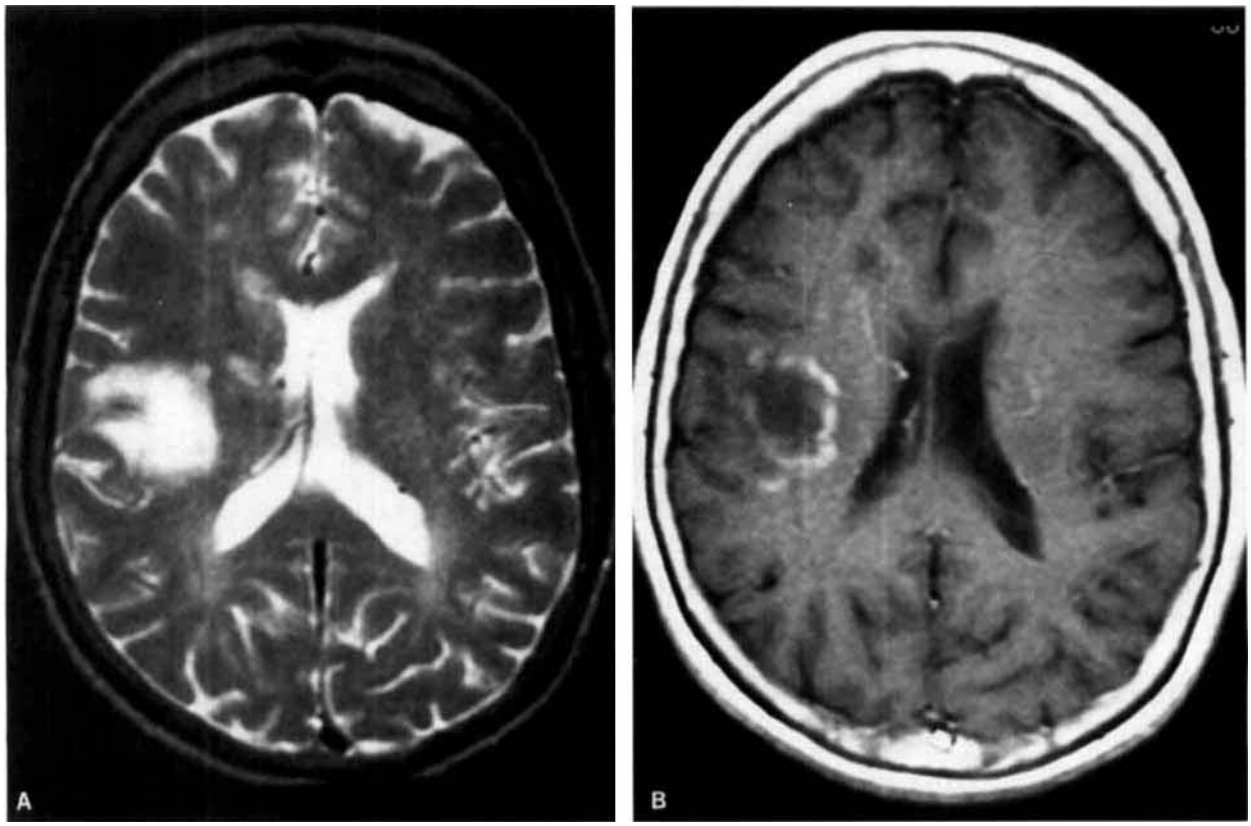

FIGURE 2. MR Image of the head at time of presentation. (**A**) T2 (TR 2500; TE 20). A focal area of abnormal T2 hyperintensity is seen at the corona radiata on the right. There are smaller scattered areas of punctate T2 hyperintensity. (**B**) T1 (TR 600; TE 17) axial MR image with gadolinium reveals peripheral ring-type enhancement about the focus of abnormal T2 hyperintensity. Note the central area of T1 hypointensity, suggestive of focally increased tissue water content.

during 5-FU and levamisole treatment. They are not included in Table 1 due to the paucity of clinical details.

In these series, all patients had primarily white matter enhancing lesions on imaging studies that appeared to be consistent with metastases. All occurred within 5 months of starting chemotherapy, and the total doses of 5-FU and levamisole received prior to the development of symptoms were quite similar. All patients improved once 5-FU and levamisole were discontinued. Most patients were treated with corticosteroids; however, the patient reported by Kimmel and Schutt[6] improved spontaneously without the use of steroids. At least three additional patients who developed leukoencephalopathy while receiving 5-FU and levamisole have resumed therapy with 5-FU alone with no recurrence of symptoms.[5,7]

A cerebral demyelination syndrome occurring in patients treated with 5-FU and levamisole may be more common than is generally appreciated. Hook et al.[3] reviewed two large trials of surgical adjuvant therapy for patients with resected colon cancer in which 1,030 patients were treated with either levamisole alone, or levamisole plus 5-FU for 1 year. Among these patients, neurologic symptoms or signs developed in 32 (5%) during treatment; 26 patients had been treated with levamisole plus 5-FU. A high incidence of CNS toxicity has also led to an interruption of accrual to North Central Cancer Treatment Group (NCCTG) and National Cancer Institute of Canada (NCIC) studies of adjuvant high dose levamisole plus 5-FU.[8] In the NCCTG study, almost 10% of the approximately 150 patients randomized to the high dose levamisole regimen experienced Grade 3 or 4 neurotoxicity, which included common symptoms of ataxia, confusion, and agitation. Symptoms became obvious as early as Day 2 after the initiation of treatment, which was given at a dose threefold higher than the conventional dose of levamisole.[8]

Both 5-FU and levamisole have been implicated in the etiology of this syndrome. Although the most common neurologic toxicity occurring with 5-FU is an acute cerebellar syndrome, occurring in up to 7% of patients,[9–12] an acute encephalopathy has been described.[13–15] Most of these patients were reported before the widespread availability of CT and MRI, and biopsy results were not given. A more severe subacute leu-

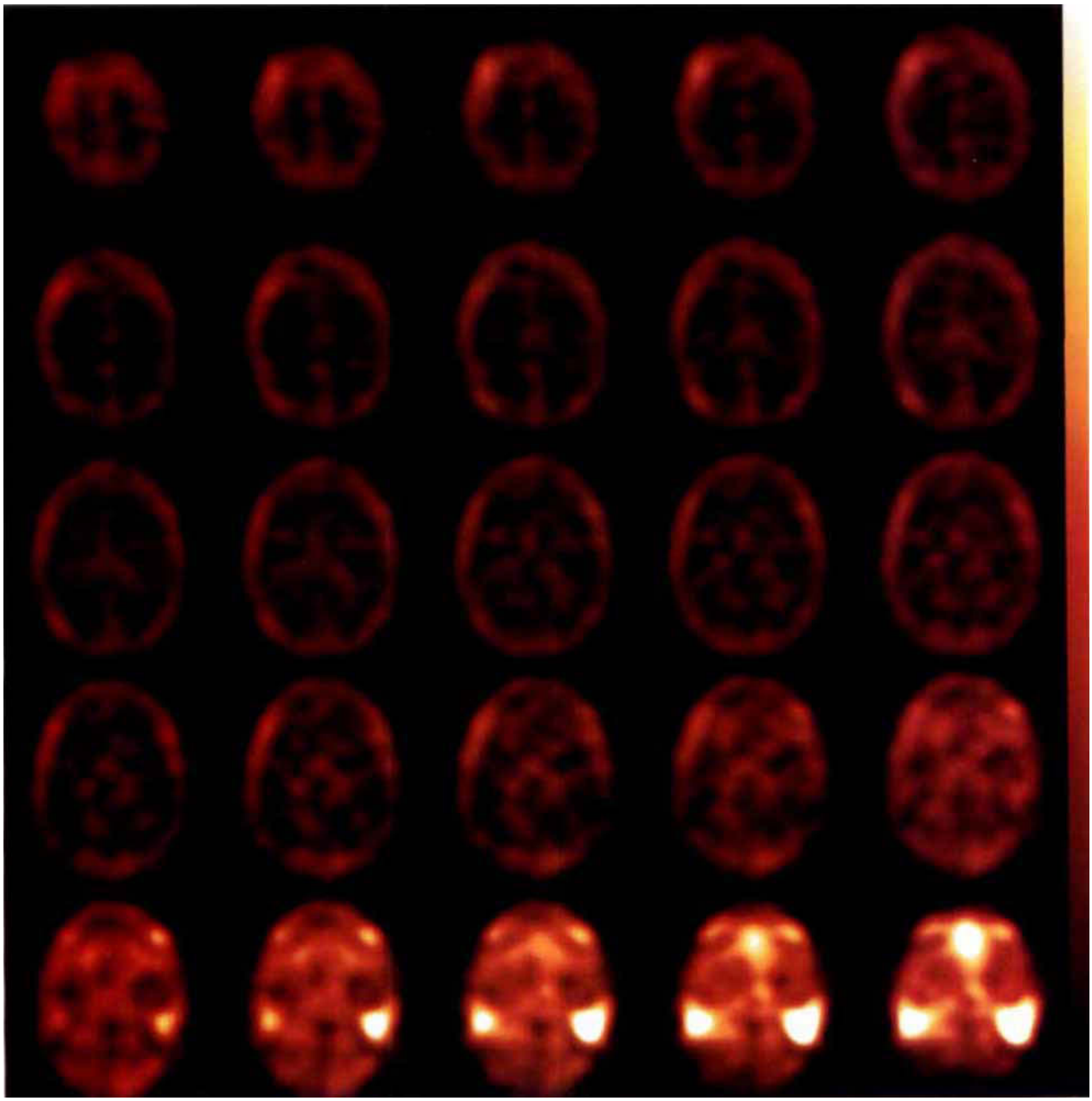

FIGURE 3. ^{201}Tl image. Multiple contiguous 7-mm-thick transaxial ^{201}Tl SPECT images demonstrate physiologic mucosal uptake in the frontal and maxillary sinus areas and a lesser degree of scalp uptake. There is no evidence of intracerebral focal uptake on these (or 2-mm-thick) images, which have been "brightened" for increased sensitivity by upper thresholding to 50%.

koencephalopathy has been reported with several 5-FU derivatives.[16–18] Neuropathologic examination in four of these cases revealed massive demyelination.[16] In another report, CT scan revealed diffuse decreased attenuation of the cerebral white matter indicative of leukoencephalopathy, but biopsies were not described.[15] Lastly, cerebral demyelination thought to be secondary to 5-FU or its metabolites has been reported in a patient with a genetic defect in pyrimidine metabolism resulting in a prolonged elimination half-life and enhanced 5-FU toxicity.[19]

Levamisole has been associated with a variety of neurologic syndromes including encephalopathy and (rarely) seizures.[20–23] In dog models, oral administration of levamisole has resulted in clear evidence of CNS demyelination.[24] Kimmel and Schutt[25] recently reported a patient with malignant melanoma who developed a cerebral demyelinating disease

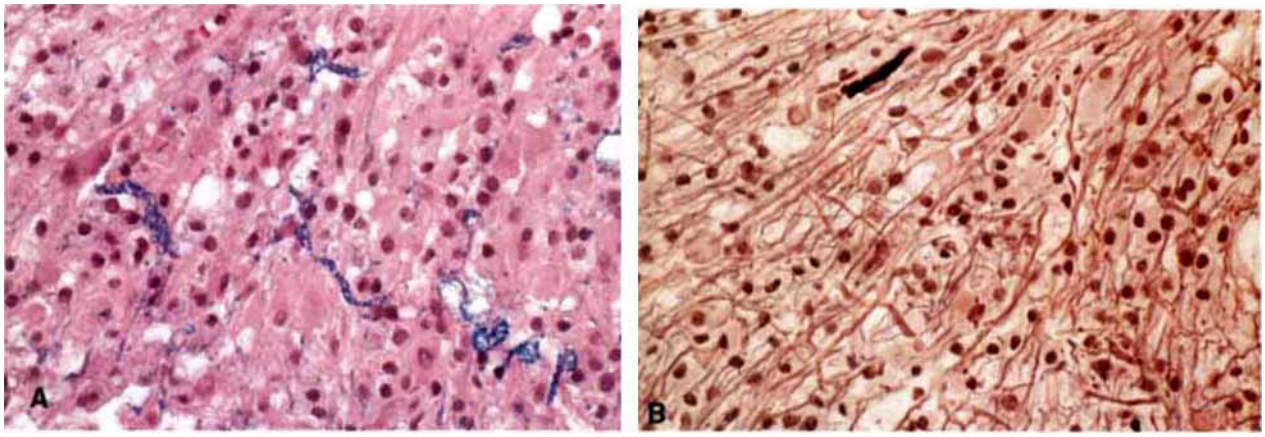

FIGURE 4. Stereotactic biopsy showing (**A**) marked loss of myelin and macrophage infiltration with (**B**) relative preservation of axons. (**A**) Luxol fast blue/H & E. 2 (**B**), Bodian (both A and B, original magnification ×100).

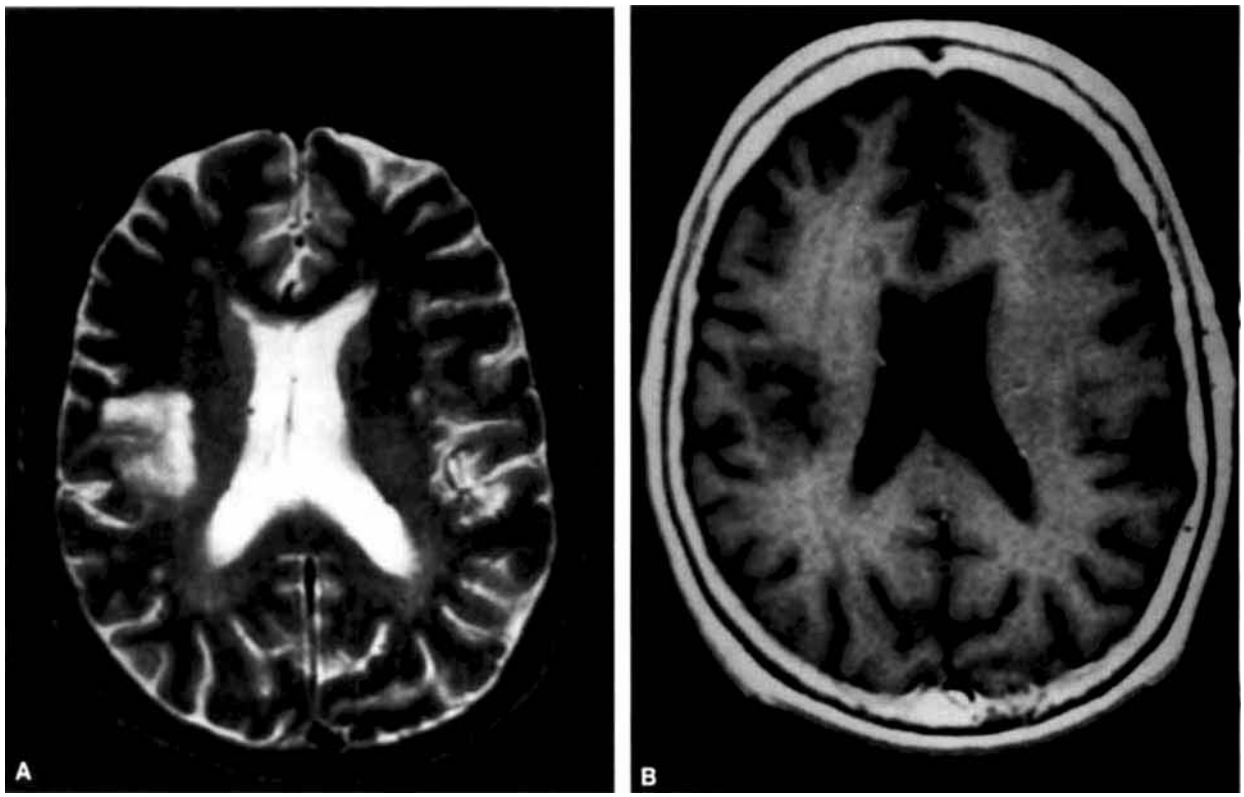

FIGURE 5. (**A**) T2-weighted (TR 2500; TE 90) axial MR image of head, 1 month after discontinuation of 5-FU and levamisole therapy, revealing diminution in volume of the focus of corona radiata T2 hyperintensity. (**B**) T1-weighted (TR 600; TE 90) axial MR image with intravenous gadolinium reveals resolution of the previously noted peripheral ring-type enhancement.

5 weeks after beginning adjuvant therapy with levamisole. The radiologic findings were similar to those reported in patients receiving 5-FU and levamisole, but a biopsy was not performed. This patient was treated with steroids and improved after discontinuation of levamisole. Further evidence that levamisole is important in the pathogenesis of this cerebral demyelinating syndrome is that at least two patients who developed cerebral demyelination after 5-FU and levamisole have been rechallenged with 5-FU alone without a recurrence of symptoms.[5,7]

TABLE 1
Summary of Case Reports Detailing 5-FU/Levamisole Neurologic Toxicity

Reference	Age (yr)/sex	5-FU (g)	LV (g)	Duration of therapy (wks)	Symptoms/signs	CT/MRI	CSF	Biopsy	Pathology	Treatment	Outcome
Hook et al., 1992[3]	68/M	9.7	2.7	15	Loss of consciousness	Multifocal enhancing white matter lesions	NR	No	N/A	Dex	Improved; lesions decreased in size within 1 mo
Hook et al., 1992[3]	45/F	12.1	3.6	18	Confusion, gait difficulty	Multifocal enhancing white matter lesions	5 cells; P 46 mg%, oligoclonal bands	Yes	Demyelination	Dex	Improved
Hook et al., 1992[3]	74/F	15.7	3.8	19	Confusion; ataxia	Multifocal enhancing and unenhancing lesions	11 cells; P 54 mg%, oligoclonal bands	Yes	Demyelination	Dex	Improved
Kimmel and Schutt, 1993[6]	74/M	9.5	2.3	8	Confusion, ataxia, diplopia	Multifocal enhancing and unenhancing lesions	NR	No	N/A	None	Improved
Fassas et al., 1994[4]	47/M	12.1	2.8	8	Confusion, agitation, dysarthria	Multifocal enhancing and unenhancing lesions	Normal	Yes	Demyelination	Dex	Improved
Chen et al., 1994[5]	68/F	5.4	1.4	9	Ataxia	Multifocal enhancing and unenhancing lesions;	No cells; P 138 mg%	Yes	Gliosis; demyelination	Dex	Improved; received 5-FU only after
Present report	68/F	8.9	1.4	14	Paresis, ataxia	Multifocal enhancing and unhancing lesions, SPECT cold	No cells; P 42 mg%	Yes	Demyelination	Dex	Improved

NR: not reported; P: cerebrospinal fluid protein; Dex: dexamethasone; 5-FU: 5-fluorouracil; LV: levamisole.

In the patient described herein, intracerebral metastatic disease was strongly considered but was considered less likely because of a normal serum CEA level and no other evidence of metastatic disease. In addition, a ^{201}Tl SPECT study was "cold" or negative in the areas of lesions. ^{201}Tl SPECT imaging is a noninvasive method that can help differentiate intracranial tumors from benign processes.[26-28] Actual uptake of ^{201}Tl into tumors appears to be related to a combination of factors, including regional blood flow, blood-brain barrier permeability, and cellular uptake. Tumor cell thallium uptake appears to be related to growth rate and an increase in Na^+K^+ ATPase activity on viable tumor cell membranes.[29-31]

Ancri et al.[28] found a higher relative uptake of ^{201}Tl in five cases of CNS metastases compared with intracerebral hematoma or infarction. An additional 25 patients with one or several metastases were studied with both ^{201}Tl and sodium pertechnetate (^{99m}Tc).[27] All cases demonstrated uptake with ^{201}Tl within 10 minutes of injection, and in five cases, small metastases invisible with ^{99m}Tc could be demonstrated with ^{201}Tl. Slizofski et al.[32] correlated thallium tumor index with histopathologic results and determined that a thallium tumor index of 2.4 or more (that is, a ratio of thallium uptake in the lesion relative to normal surrounding brain parenchyma) was useful for predicting malignancy in patients with both primary and metastatic carcinomas. In our patient, the thallium tumor index was less than 1.0.

Although falsely negative studies[32] are uncommon with ^{201}Tl SPECT, tumor extent may be underestimated in some patients, especially those with lymphoma.[33] Yoshii et al.[34] studied 11 cases of metastatic tumor and found that ^{201}Tl SPECT failed to diagnose only one case and another case with several small tumors of less than 1.5 cm in diameter, for a false-negative rate of 9%. Dierckz et al.[35] evaluated 14 patients with brain metastases and found that thallium scanning was falsely negative for a pontine metastasis in one patient, and it underestimated the presence of four additional metastases, less than approximately 1.5 cm in diameter, in two additional patients. In that study, the relative sensitivity of ^{201}Tl SPECT for supratentorial brain tumors was 71.7%, and specificity was 80.9%.[35] False-positive studies are also uncommon. Some conventional meningiomas have consistently shown thallium avidity with indices greater than 1.5, and thallium localization at sites of abscess, infarction, and hemorrhage have been reported.[28,34,35-37]

Since adjuvant treatment with 5-FU and levamisole has become the standard therapy for Stage III colon carcinoma, the number of patients potentially exposed to this drug combination each year is substantial. It is likely that this cerebral demyelination syndrome is being underdiagnosed. In the patient we have reported, the atypical radiographic appearance of the lesions in conjunction with other clinical parameters (a low CEA level) raised the suspicion of a nonmetastatic process; ^{201}Tl SPECT further increased this suspicion. This patient's clinical course was identical to that of the several patients who have been reported in the literature with cerebral demyelinating syndrome secondary to 5-FU and levamisole.

The importance of recognizing 5-FU/levamisole-induced leukoencephalopathy must be emphasized. The differential diagnosis of multiple intracranial white matter lesions in a patient such as this includes metastatic intracranial carcinoma, multicentric gliomas, primary CNS lymphoma or toxoplasmosis, progressive multifocal leukoencephalopathy, and diffuse necrotizing leukoencephalopathy associated with chemotherapy[38] or immunosuppression.[39] A neurologically symptomatic cancer patient with multiple contrast enhancing lesions on MRI may be presumed to have cerebral metastasis and may receive cranial irradiation without benefit of a brain biopsy. Clinical diagnosis of metastatic disease without biopsy may have led to devastating results in our patient; radiation may be especially injurious to patients with demyelinating disease.[40] In patients who present typically after receiving several months of 5-FU and levamisole chemotherapy, the use of ^{201}Tl SPECT may be useful to make the distinction between malignant and nonmalignant disease, noninvasively. Stereotactic biopsy, a relatively simple and safe procedure, may be necessary to resolve the issue and lead to treatment modifications. We would recommend that every patient who receives therapy with 5-FU and levamisole, and who develops neurologic symptoms with multifocal lesions on imaging studies, be carefully evaluated for the presence of potential brain metastases. If a question exists as to the diagnosis, we would suggest the use of ^{201}Tl SPECT to support the diagnosis. Stereotactic biopsy may be necessary to make a definitive diagnosis.

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