Multifocal Inflammatory Leukoencephalopathy Associated with Levamisole and 5-Fluorouracil: Case Report

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LEVAMISOLE AND 5-FLUOROURACIL have now become the standard chemotherapeutic regimen for patients with Stage III colon carcinoma. A case of multifocal inflammatory leukoencephalopathy secondary to levamisole alone or combination of levamisole and 5-fluorouracil is reported. Magnetic resonance imaging with gadolinium demonstrated multifocal contrast-enhancing frontal, parietal, occipital, and periventricular white matter lesions. A stereotactic biopsy revealed reactive gliosis and macrophage infiltration, without evidence of metastatic tumor. Despite continuation of 5-fluorouracil, resolution of contrast-enhancing lesions on magnetic resonance imaging without further neurological sequelae occurred when levamisole was stopped. The patient died with evidence of systemic metastasis 6 months later. Autopsy examination of the brain revealed multifocal demyelinating lesions, with no evidence of metastatic tumor. Immunoperoxidase studies of demyelinated lesions demonstrated infiltrating macrophages strongly positive for Class II antigens, interleukin-6, and interleukin-1α. Surrounding astrocytes were positive for granulocyte macrophage colony-stimulating factor. Small numbers of perivascular T cells were present. This patient represents the first autopsy documented case of levamisole associated multifocal inflammatory leukoencephalopathy. (Neurosurgery 35:1138–1143, 1994)

Key words: Autopsy, Levamisole, Multifocal inflammatory leukoencephalopathy

Levamisole is a phenylimidothiazole, which was introduced in 1965 as an antihelminthic (15). Since then, it has attracted interest as a chemotherapeutic agent because of its presumed immunostimulatory activity (9, 25). In conjuction with 5-fluorouracil (5-FU), levamisole has been shown to decrease the risk of clinical recurrence and to increase the survival of patients with Stage III colon carcinoma (18, 21, 23). Well-documented signs and symptoms of levamisole toxicity have included diarrhea, reversible agranulocytosis, leukopenia, headache, confusion, myalgia, and tremor (6, 23, 25, 31). Recently, four patients with reversible mutifocal inflammatory leukoencephalopathy after treatment with 5-FU and levamisole have been reported. The authors concluded that the cause was most likely secondary to 5-FU; however, levamisole toxicity could not be ruled out (14, 16). We have recently encountered another case of multifocal inflammatory leukoencephalopathy, which is unique in that: 1) multifocal inflammatory leukoencephalopathy seemed to be secondary to levamisole alone or a combination of levamisole and 5-FU; 2) autopsy findings showed multiple cavitary white matter lesions with axonal loss as well as demyelination; and 3) immunohistochemistry studies suggested that the demyelination was associated with macrophage activation.

CASE REPORT

A 68-year-old right-handed Japanese woman underwent primary resection of a Stage III colon carcinoma. She was entered into the Southwest Oncology Group Protocol 8899 to determine her postoperative adjuvant therapy. After randomization, she received 450 mg/m^2 of 5-FU i.v. daily for 5 days, followed by 4 weeks of a 450-mg/m^2 5-FU bolus every week. Levamisole was given orally 150 mg daily for 3 days every 2 weeks. It was administered concomitantly with 5-FU for 3 days at the beginning of the regimen and every 2 weeks when 5-FU was given as a bolus at the beginning of the week. Within hours of levamisole administration, she complained of feeling drunk and confused, lasting for the duration of her levamisole therapy and recovering within 24 hours. Levamisole was used for 8 weeks; however, it was stopped secondary to continued complaints of lethargy, disorientation, expressive dysphasia, and short-term memory loss.

Ten days after levamisole discontinuation, the patient was subsequently admitted with progressively poor balance and weakness and numbness of her left leg. On initial examination, she was afebrile, alert, and oriented, but had a mild expressive dysphasia. No cranial nerve abnormalities were detected. Motor examination showed 5–/5 strength in her left leg, normal elsewhere. Her gait was moderately ataxic, with a tendency to fall to the right. Sensation was intact to pin prick throughout; however, she did have a subjective sensation of numbness in her left leg. Computed tomography re-

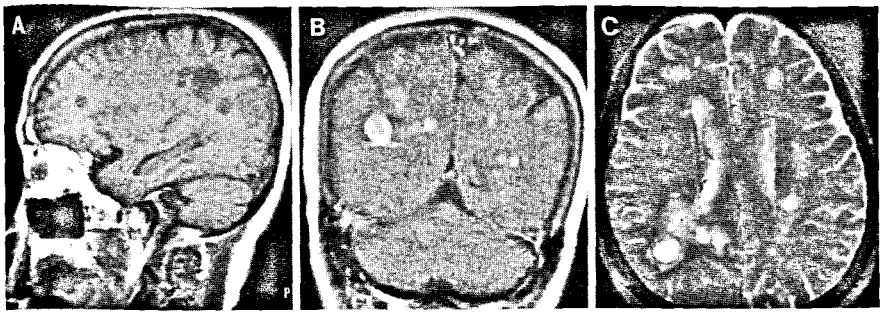

FIGURE 1. MRI scan (T1-weighted with gadolinium enhancement) shows multiple contrast-enhancing frontal, parietal, occipital, and periventricular white matter lesions (*B*) hypointense to gray matter on T1-weighted images (*A*) and hyperintense to gray matter on T2-weighted images (*C*).

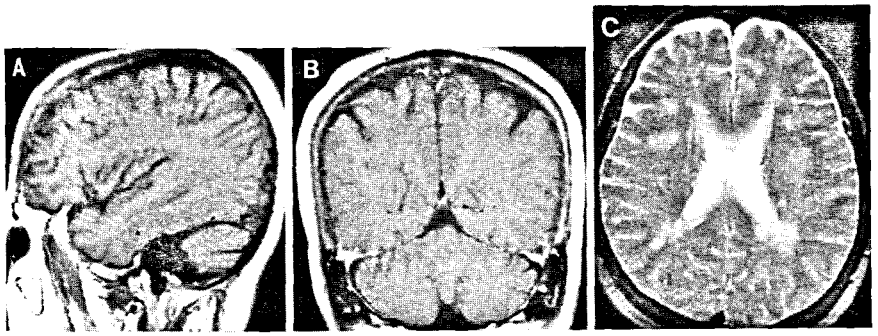

FIGURE 2. MRI scan of corresponding images in *Figure 1* shows resolution of contrast-enhancing lesions on T1-weighted images on discontinuation of levamisole (*A* and *B*). Residual lesions may be seen on T2-weighted images (*C*).

vealed multiple contrast-enhancing frontal, parietal, occipital, and periventricular intracranial white matter lesions. Magnetic resonance imaging (MRI) showed multiple enhancing white matter lesions that were hypointense to gray matter on T1-weighted images and hyperintense to gray matter on T2-weighted images (*Fig. 1, A–C*). Initial differential diagnosis included intracranial metastasis secondary to primary colon adenocarcinoma versus an infectious cause. Her admitting white blood cell count was 6.3×10^3 cells/ml. Her cerebrospinal fluid (CSF) cell count was unremarkable; CSF protein was 138 mg/dl, and glucose was 58 mg/dl. Gram stain showed 1+ PMNs, 1+ monocytes, and no organisms. CSF cytology, bacterial cultures, toxoplasmosis titers, and cryptococcal titers were negative. CSF oligoclonal bands and immunoglobulin G index were not available. A metastatic workup, including computed tomography of the chest and abdomen, showed no additional lesions.

A stereotactic biopsy was performed on an enhancing right parietal lesion. The biopsy revealed atypical reactive gliosis admixed with foamy macrophages, suggesting demyelination; however, no definitive demyelination could be documented. Postoperatively, the patient was placed on dexamethasone (16 mg/day), which was tapered over 1 month. Her chemotherapy regimen of 5-FU and levamisole was discontinued. She had a dramatic improvement at home, with improvement in her mental status and motor strength. Repeat MRI 1 month later showed resolution of her enhancing multifocal white matter lesions on T1-weighted images; however, a few residual lesions were seen on T2-weighted images (*Fig. 2, A–C*). The patient again began receiving 5-FU 6 weeks after her initial biopsy. At that time, her mental status was normal, with a nonfocal neurological examination. Additional MRI scans of the brain 1 and 4 months after initiation of 5-FU continued to show residual nonenhancing lesions on T2-weighted images only.

The patient died with evidence of widespread systemic metastasis 6 months later. Neuropathological examination of the brain revealed multifocal demyelinating lesions within the white matter of the cerebral hemispheres, including the corona radiata, optic radiations, cingulum, and temporal lobe, several of which were cavitary, with no evidence of metastatic tumor (*Fig. 3A*).

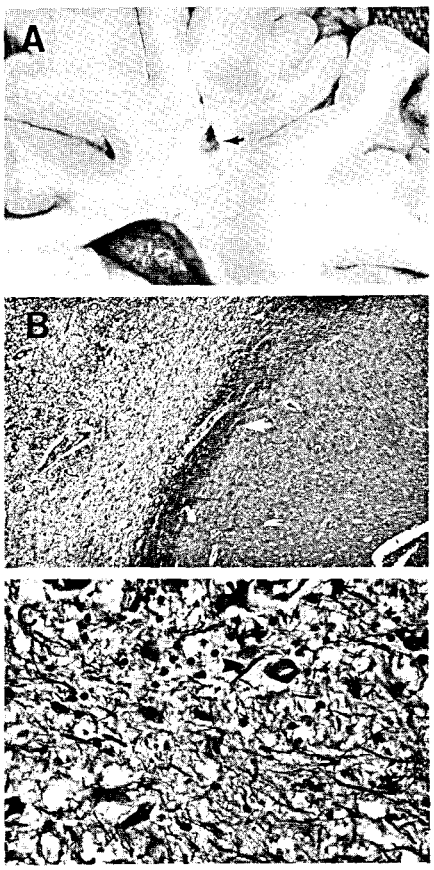

FIGURE 3. Coronal sections of the formalin-fixed brain show numerous tan-to-yellow softened areas within the white matter of the cerebral hemispheres, including the corona radiata, optic radiations, cingulum, and temporal lobe white matter. One of the cavitary lesions within the right corona radiata is shown (*A, arrow*). Silver stains of demyelinated lesions show axonal depletion. Note the sparing of the U fibers (*B, arrow*). At higher magnification, residual axons are identified in the center of a demyelinated lesion (*C, arrowhead*).

Microscopic examination of the lesions demonstrated well-demarcated areas of extensive gliosis. In the subcortical white matter, these areas extended to but did not involve the Mynert U fibers (*Fig. 3B*). Associated astrocytes were enlarged and occasionally bizarre in morphology. A myelin stain (Luxol fast blue) of representative lesions showed extensive demyelination (*Fig. 3B*). A silver axonal stain (modified Bielschowsky) showed moderate loss of axons, although intact axons were identified in the midst of extensive myelin loss (*Fig. 3C*). Electron microscopy of the lesions showed myelin debris, numerous astrocytic processes, and rare thinly myelinated axons. There was no evidence of active demyelination. No viral particles were identified.

Immunohistochemical staining was performed on cryostat frozen sections of brain dissected at autopsy, which contained a demyelinated lesion as previously described (4). Numerous reactive astrocytes (glial fibrillary acidic protein+, Biogenics, San Ramon, CA), macrophages (CD 11c+, Becton-Dickinson, San Jose, CA) (*Fig. 4A*), and small numbers of perivascular T cells (CD 4+ and CD 8+, Becton-Dickinson) were present in the areas of demyelination. Macrophages were strongly positive for Class II antigens (Becton-Dickinson) (*Fig. 4B*), interleukin-6 (IL-6; Genzyme, Cambridge, MA) (*Fig. 4C*), and IL-1-α (Genzyme, Cambridge, MA). Tumor necrosis factor-α (TNF-α; Genzyme) was very weakly positive in macrophages. Reactive astrocytes were strongly positive for granulocyte macrophage colony-stimulating factor (Genzyme) (*Fig. 4D*). Immunoperoxidase staining for Ki-67 (Dako, Carpinteria, CA), a proliferation-associated antigen, demonstrated very rare immunoreactive glial nuclei. An immunohistochemical stain for the JC virus (a kind gift of Dr. Duard Walker, University of Wisconsin, Madison, WI), a strain of polyomavirus associated with progressive multifocal leukoencephalopathy, showed no reactivity.

DISCUSSION

This patient represents a clearly documented case of multifocal inflammatory leukoencephalopathy associated with administration of levamisole alone or in combination with 5-FU. Unlike the previously reported cases, our patient had selective discontinuation of levamisole and continuation of 5-FU, with resolution clinically and radiographically of her intracranial lesions (14, 16). This is the first autopsy case of multifocal inflammatory leukoencephalopathy, and it demonstrates that the demyelinated plaques not only have axonal depletion, but cavitary changes as well. These cavitary changes, although nonenhancing on T1-weighted images, are seen as residual regions of hyperintensity on T2-weighted images, similar to those reported by Kimmell et al. (16).

The differential diagnosis of multiple intracranial white matter lesions in a patient such as this is varied. The possiblity of metastatic intracranial colon carcinoma, although unusual without obvious systemic involvement, must be ruled out. Multicentric gliomas, primary central nervous system lymphoma, or toxoplasmosis must be considered (8, 11, 19, 20). Progressive multifocal leukoencepathology, although now reported predominantly in patients with acquired immunodeficiency syndrome, also must be considered (7). Last, the diagnosis of diffuse necrotizing leukoencephalopathy secondary to chemotherapy must be considered (27, 28). Intrathecal methotrexate or high-dose parenteral methotrexate, especially when combined with intracranial radiation, has been the most widely recognized chemotherapeutic agent causing multifocal inflammatory leukoencephalopathy (1, 22, 27). Estimated incidence ranges from less than 1% to 45%, depending on the mode of therapy. Unlike levamisole, symptom onset earlier than 3 months after treatment is unusual. 5-FU has been reported to cause pancerebellar dysfunction, encephalopathy, and peripheral neuropathy, and derivatives of 5-FU have been reported to cause reversible leukoencephalopathies (17, 26, 29). The present study suggests that this patient, as well as the four previously reported cases with multifocal inflammatory leukoencephalopathy, had levamisole-induced lesions. No other signs or symptoms of levamisole toxicity, such as agranulocytosis, leukopenia, or severe gastrointestinal problems, were present in this patient.

The radiological and pathological findings of multifocal inflammatory leukoencephalopathy secondary to levamisole have been well documented. On MRI, the lesions are predominantly supratentorial, periventricular, and enhancing after gadolinium administration (14). On light and electron microscopy, a demyelinating lesion, with axonal preservation, is seen. Reactive astrocytes, macrophage infiltration with a moderate

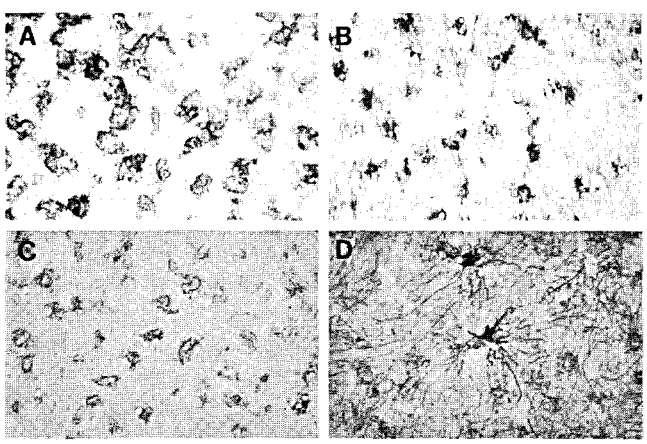

FIGURE 4. Immunoperoxidase studies of demyelinated lesions reveal scattered infiltrating CD 8+ cells within the parenchyma (not shown), as well as numerous CD 11c+ macrophages (*A*). The macrophages show prominent Class II antigen expression (*B*). Numerous macrophages were strongly positive for IL-6 (*C*) and IL-1α (not shown). TNF-α was only weakly positive in occassional macrophages (not shown). Granulocyte macrophage colony-stimulating factor was localized prominently to morphologically identifiable astrocytes (*D*).

number of lymphocytes, and oligodendrocytes at the edge of the demyelinating lesion are present (14, 16).

Although the ultrastructural changes of multifocal inflammatory leukoencephalopathy have been reported, the mechanism by which levamisole induces these lesions is unknown. Levamisole is thought to have an immunorestorative effect by increasing antigen response and potentiating the functions of lymphocytes, macrophages, and granulocytes (30). It increases delayed-type hypersensitivity in humans; however, no direct effects on B lymphocytes or antibody production are present (10). In mammalian cells, levamisole displays both cholinergic and antioxidant properties, alters nucleotide levels, and inhibits alkaline phosphatase (9). It seems to decrease metastasis formation in slowly growing tumors, especially when used as an adjuvant to cytoreductive treatment (5).

To explore the presumed immune-mediated action of levamisole, immunohistochemical stains for leukocytes and cytokines were performed. At the time of autopsy, the patient had been neurologically asymptomatic for approximately 6 months. The presence of activated leukocyte infiltration with production of proinflammatory cytokines (IL-1α, IL-6, and TNF-α) suggests that these lesions, although morphologically quiescent, are still immunologically active. TNF-α has been reported to be associated with myelin degeneration and astrocytic degeneration (13). The finding of only small amounts of TNF-α is consistent, therefore, with the lack of ongoing demyelination. The production of granulocyte macrophage colony-stimulating factor by reactive astrocytes also may contribute to the immune response by attracting macrophages to the lesion (2). The finding of white matter demyelination associated with gliosis, macrophage, and T cell infiltration is similar to that found at the periphery of multiple sclerosis plaques. Immunohistochemical studies of chronic active multiple sclerosis lesions have documented the presence of activated astrocytes and macrophages, with production of Class II, TNF-α, IL-1α, and IL-2, findings similar to this case (12, 13). Although TNF-α is more prominent in chronic active multiple sclerosis, we do not know whether TNF-α would be more prominent early in the course of multifocal inflammatory leukoencephalopathy.

Inasmuch as 5-FU and levamisole have become the standard postoperative adjuvant therapy for patients with Stage III carcinoma of the colon, this combination may be initiated for 25,000 patients in the United States in 1993 (3, 23). In a patient treated with levamisole presenting with focal neurological deficits and radiographic evidence of multiple enhancing white matter lesions, the possibility of drug-induced leukoencephalopathy must be considered in the differential diagnosis. Rapid diagnosis is essential, because demyelinating lesions potentially develop into permanent lesions with axonal depletion and cavitary changes. Concomitant administration of glucocorticoids may result in more rapid clinical and radiographic resolution of multifocal inflammatory leukoencephalopathy (16).

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COMMENTS

Because 5-fluorouracil (5-FU) and Levamisole have become standard therapy for Stage III colonic carcinoma, one of the most frequent forms of cancer, the number of patients exposed to this drug combination each year is substantial. Therefore, it is important to raise awareness of the possible adverse effects, even if they are infrequent.

The differential diagnosis in a patient with cancer and encephalopatic symptoms with white matter lesions include a wide variety of diseases. Metastases are always important considerations, because they may present in varied forms. Direct and indirect effects of treatment are also major possibilities. Cranial irradiation can produce cerebral lesions with involvement of the microvasculature or even large vessels. Chemotherapy is another well-known cause of white matter disease; the best known example is diffuse necrotizing leukoencephalopathy in association with methotrexate, but other agents including biological response modifiers (interferons and interleukins) also can cause white matter lesions. Immunosuppression, related to therapy or to the neoplasm itself, predisposes a patient to infectious diseases (e.g., progressive multifocal leukoencephalopathy and toxoplasmosis) and to tumors such as primary central nervous system lymphoma. An intriguing form of necrotizing multifocal leukoencephalopathy has been described in association with immunosuppression; the pathogenesis is unknown, and it is usually confined to the basis pontis, although it also may involve additionally the white matter of the cerebral hemispheres (2).

Neurotoxicity associated with 5-FU has been well described. The most frequent well-defined neurological syndrome is pancerebellar dysfunction of sudden onset with gait ataxia, appendicular discoordination, dysarthria, and nystagmus. More rare are the syndromes of encephalopathy (headaches, confusion, disorientation, lethargy, and seizures) and peripheral neuropathy. 5-FU derivatives have been implicated in cases of encephalopathy with white matter abnormalities; however, they tend to be more diffuse and without evidence of inflammation (3). Experimental models of 5-FU toxicity implicate metabolites of the drug in the production of the lesions: α-fluoro β-alanine seems to be particularly toxic.

The pathology of these lesions consists of vacuolation caused by myelin dysruption in the cerebellum, brain stem, and cerebral white matter; there also may be associated necrosis, especially in the brain stem, but inflammation is not a feature (7). Although most 5-FU is eliminated in the urine unchanged, a small percentage (about 10%) is metabolized in the liver, and it may generate the toxic metabolites. It is reasonable to speculate that levamisole might alter the pharmacokinetics of 5-FU and increase the proportion that is metabolized by the liver. The use of levamisole alone has been reported to produce unspecific neurological symptoms, which include fatigue, taste change, arthralgia/myalgia, headaches, dizziness, anxiety, and irritability. Symptoms usually improve after drug administration is discontinued (6). Chen et al. contribute with the description of a new case of inflammatory multifocal leukoencephalopathy associated with this therapy. They present the first autopsy study of this disease and suggest that pathogenesis would be related more to Levamisole rather than to 5-FU.

It is possible that this syndrome is more frequent than is apparent, because subclinical forms of milder disease may be unnoticed. Neurological symptoms have been described in about 18% of patients treated with this drug combination; most of them were vague, mild, and resolved spontaneously after ceasing therapy (6). It is conceivable that at least some of these cases, if studied with magnetic resonance imaging, may have had lesions similar to the ones described in this and in previous papers (4, 5).

Leukoencephalopathy associated with chemotherapy has been well described. It has been related mostly, but not exclusively, to methotrexate, especially when combined with brain radiation (8). However, this diffuse necrotizing leukoencephalopathy is a different entity to the one described by Chen et al., which is an inflammatory demyelinating leukoencephalopathy. Although they may look radiologically similar because of a similar pattern of lesion distribution, diffuse necrotizing leukoencephalopathy is characterized by necrosis and swelling of axons, with inconsistent spatial relationship to blood vessels and very little evidence of inflammation. In contrast, the disease discussed here is a perivascular inflammatory process, with prominent demyelination and some degree of axonal disruption of axons. Histopathology and immunohistochemistry are reminiscent of the findings described in multiple sclerosis (1). This is intriguing, considering that the syndrome could be caused by the levamisole component of the chemotherapy. Levamisole has well-described immunomodulatory stimulant effects. In vivo human studies have founded increased dinitrochlorobenzene skin test reactivity, increased lymphocyte proliferation to mitogens, and increased expression of neutrophil Fc receptors (9). An interesting possibility would be the application of the use of levamisole to develop a more adequate animal model to further understand multiple sclerosis. The role of steroids in the treatment of levamisole- and 5-FU-associated leukoencephalopathy is uncertain, because most cases have received steroids; however, one patient

who did not receive treatment presented clinical and radiological improvement as well.

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In patients with known cancer, the presence of a single supratentorial enhancing mass lesion has approximately a 90% probability of representing a metastasis (1). This probability is expectedly even higher in patients with multiple masses.

This report describes an unusual occurrence of leukoencephalopathy, presumably caused by levamisole (but not necessarily so), and the presence of multiple lesions on magnetic resonance imaging that can and should be considered metastatic in nature until proved otherwise. The systematic use of whole-brain radiation therapy without biopsy in such patients is unfortunately not rare, and this example again emphasizes the advantages and simplicity of stereotactic biopsies in providing the necessary information for optimal therapeutic decision making. The authors' excellent follow-up, including the autopsy results, is exemplary.

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