Dear Sir,

Multifocal inflammatory leukoencephalopathy (MIL), a central nervous system disorder characterized by demyelination with perivascular inflammation, has recently been reported in several patients treated with the combination of fluorouracil (FU) and levamisole chemotherapy [1–9]. However, there have been no reports mentioning spinal lesions, whereas demyelinating lesions have been frequently found in other diseases such as multiple sclerosis (MS), acute transverse myelitis, and acute disseminated encephalomyelitis.

We report the first case of a patient with acute disseminated encephalomyelitis associated with 5-FU and l-leucovorin treatment and discuss its putative pathogenesis.

Case Report

A 55-year-old Japanese man underwent primary resection of stage III colon carcinoma. Three months later, he received adjuvant therapy with 500 mg of 5-FU and 50 mg of l-leucovorin i.v. daily for 5 days. Immediately after this treatment had finished, he began to complain of dysesthesia of his legs and difficulty in urination. Following that, he could not walk due to muscle weakness, and was admitted to our hospital. Neurological examination revealed muscle weakness of legs, sensory disturbance below T7 level, and diffuse hyperreflexia except for jaw jerk. The Babinski reflexes were bilaterally positive. He needed a urinary catheter due to urinary retention problems. Routine laboratory examination was normal except for an erythrocyte sedimentation rate of 17 mm in 1 h. Both HIV and HTLV-1 serum antibodies were negative. Tumor markers, such as CEA and CA19-9, were in the normal range. Cerebrospinal fluid examination showed the increased cell count of 42 cells/μl and elevated protein of 61 mg/dl. The IgG index was at the upper limit of the normal range at 0.7, suggesting that intrathecal synthesis of IgG did not increase significantly. Myelin basic protein was increased at 489 pg/ml. All bacterial, fungal, and viral cultures were negative. Repeated cytology was negative. Genotyping for HLA showed that he had DRB1*1501 and DQB1*0602.

MRI of the spine revealed multiple hyperintense lesions throughout C3–5, T2–3, 9–12 and conus medullaris on T2-weighted images (fig. 1). Those lesions mostly exhibited multiple enhancements after intravenous administration of gadolinium. Only a small hyperintense lesion was seen in the brain white matter without gadolinium enhancement (fig. 2).

The patient was intravenously given methylprednisolone, 1,000 mg/day for 3 days, followed by prednisolone orally, 50 mg/day. The dose was tapered off over 4 weeks. As soon as the treatment began, his neurological status began to get better. At the end of therapy, he was able to walk without any difficulty, and dysesthesia of legs had disappeared. He no longer needed to use a urinary catheter. Five months later, follow-up MRI revealed no hyperintense lesions in his spinal cord but only a small T2 hyperintense lesion in the deep white matter that was the same as the one that had been detected on the first cerebral MRI. He did not have any attacks until he died of recurrent colon cancer after a period of 8 months.

Discussion

The pathogenesis of the neurological disorder in our patient is unclear. The differential diagnosis of multiple spinal cord lesions in a patient such as this includes metastatic tumors, primary CNS lymphoma, MS, sarcoidosis, collagen disease, and paraneoplastic syndrome. Laboratory tests, including cerebrospinal fluid tests and radiologic examination, provided no evidence of metastatic cancer or primary CNS lymphoma. He possibly had an idiopathic demyelinating disorder such as MS or neuromyelitis optica. However, his clinical presentation and MRI findings did not fulfill the diagnostic criteria of MS [10]. Neuromyelitis optica was also unlikely since this patient never had optic neuritis and, on spi-
Acute Disseminated Myelitis Associated with 5-FU and l-Leucovorin Treatment


nal cord MRI, did not have lesions that extended over three vertebral levels [11]. We believe that this syndrome closely resembled MIL described in patients who have received adjuvant therapy with both 5-FU and levamisole for adenocarcinoma of the colon. MIL is characterized by demyelinated lesions demonstrating infiltrating macrophages strongly positive for class II antigens, interleukin-6, and interleukin-1α [2]. This finding was similar to that found at the periphery of MS plaques [2]. These histologic examinations and good response to corticosteroid therapy indicated that its pathogenesis might have been an immune-mediated process. So far, whether 5-FU causes the disease remains controversial [3, 6]. Our patient did not receive levamisole, further suggesting that 5-FU, rather than levamisole, is responsible for MIL.

In our case, however, most of the demyelinating lesions were found in the spinal cord rather than white matter of brain. Previous reports of MIL have not mentioned spinal cord lesions. This implies that in our patient acute disseminated myelitis may be a distinct disorder from MIL.

Lucchinetti et al. [12] reported that 5-FU and levamisole exacerbated demyelination in mice infected with Theiler’s virus and concluded that they might enhance a pathologic immune response toward a persistent antigen capable of producing demyelinating disease in a susceptible host. Since our patient had DRB1*1501 and DQB1*0602, which is the HLA genotype commonly seen in European patients with conventional MS [13], we hypothesize that he is a susceptible host and 5-FU and l-leucovorin may stimulate a destructive immune response.

In conclusion, we reported a patient with acute disseminated encephalomyelitis associated with 5-FU and l-leucovorin therapy and showed that he had the HLA genotype commonly seen in conventional MS. We believe that the pathogenesis may be an immune-mediated process similar to MIL, which has pathological findings in common with MS.

Acknowledgement

We thank Dr. T. Kamata (Tokyo Metropolitan Bokutoh Hospital) and Dr. John Ludovic Croxford (National Center of Neurology and Psychiatry) for their critical reading the manuscript.

References


Fig. 1. a T2-weighted image of the cervical spine showed a hyperintense lesion throughout C3–5. Gadolinium-enhanced T1-weighted images of thoracic spine (b, c) and of lumber spine (d) revealed multiple hyperintense lesions throughout T2–3, 9–12 and conus medullaris.

In conclusion, we reported a patient with acute disseminated encephalomyelitis associated with 5-FU and l-leucovorin therapy and showed that he had the HLA genotype commonly seen in conventional MS. We believe that the pathogenesis may be an immune-mediated process similar to MIL, which has pathological findings in common with MS.

Acknowledgement

We thank Dr. T. Kamata (Tokyo Metropolitan Bokutoh Hospital) and Dr. John Ludovic Croxford (National Center of Neurology and Psychiatry) for their critical reading the manuscript.

References


