5-Fluorouracil- and Levamisole-Associated Multifocal Leukoencephalopathy

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We describe two cases of cerebral demyelination during 5-fluorouracil (5-FU) and levamisole chemotherapy following surgery for colon adenocarcinoma.

Case Reports

Case 1. A 61-year-old female, without prior neurologic history, had a resection due to colon cancer classified as Dukes stage B2. Adjuvant chemotherapy with 5-FU (450 mg/m² i.v. daily for 5 days) and levamisole (250 mg orally for 6 days) was initiated 1 month after surgery. Cycles were repeated at 4-week intervals. Ten days after the third course the patient was admitted because of confusion, dysarthria, ataxia and right hemiparesis. Meningeal signs and fever were absent. EEG was slowed bilaterally. Remote malignancies, viral, bacterial and fungal infections were ruled out. In CSF, DNA amplification for EBV, JCV, CMV and HSV was negative. MRI showed multiple, irregularly confluent, white-matter lesions, hyperintense in T2-weighted images; cerebellar hemispheres and peduncles were also affected. Chemotherapy was discontinued; dexamethasone, 12 mg i.v. daily, was given. Within a week, the patient’s conditions deteriorated to coma, with intermittent seizures, and respiratory distress. Dexamethasone was tapered over a 3-month period. The patient improved, but global aphasia and quadriplegia persisted.

Case 2. This previously healthy 54-year-old woman underwent a colectomy because of colon adenocarcinoma classified as Dukes stage C. After surgery, chemotherapy consisted of 5-FU (370 mg/m² i.v. days 1–5), oral levamisole (150 mg daily for 6 days) and leucovorin (100 mg/m² i.v. for 5 days). The cycle was repeated twice at 4-week intervals. Twenty days after the second course, the patient exhibited ataxia, difficulty in naming and repetition, hyporeflexive right limb weakness, and an impaired visual field to the right. Viral, bacterial and fungal infections were excluded. EEG showed bilateral 6-activity. CSF contained 20 lymphocytes/mm³, normal glucose, protein, and three oligoclonal bands. DNA amplification for JCV, HSV, EBV and CMV was negative in CSF. Gadolinium-DPTA MRI revealed T2 high-signal multiple lesions, sparing the corpus callosum (fig. 1a). Dexamethasone was given intravenously at 12 mg daily. Within 2 weeks, the patient’s neurologic condition improved and the steroid was tapered over 2 months. When discharged, the patient was alert and oriented, but naming and repetition were still impaired. At follow-up 2 months later, MRI lesions were less marked and confluent than previously (fig. 1b), often with enhancement after gadolinium.

Discussion

The pathogenesis of the neurologic disorder in our patients is unclear. In both, onset of neurological signs was within 2.5 months since the beginning of 5-FU and levamisole chemotherapy. Metastasis, systemic or immunocompromising illness, as well as viral and bacterial etiology were excluded. Both patients had no prior neurologic history. On account of MRI findings, PML was an alternative.
Okeda et al. [10] proposed a toxic effect on myelin due to 5-FU and its metabolites followed by an immune response to damaged myelin due to Levamisole [4]. Reviewing the literature (table 1), unsolved problems become apparent, e.g. whether recovery was due to cessation of chemotherapy or to steroid treatment or independent of both, and why some cases recovered partially. Physicians involved in trials for cancer patients should be aware of the possible link between these drugs and demyelinating disorders.

Kimmel et al. [3] reported a case treated with levamisole alone. Bozik and Gilbert [6] considered levamisole probably responsible for alterations in the blood-brain barrier, causing demyelination and reactive gliosis and macrophage infiltration in susceptible patients. Levamisole is an antihelminthic drug, used in trials for cancer, MS and rheumatoid arthritis. It induces vasculitis due to circulating immune complexes [8] and enhances antibody response by increasing delayed-type hypersensitivity [5]. Levamisole toxicity has been documented by experimental works with demyelination and infiltration around brain veins and capillaries [9]. Hook et al. [1] observed in their patients a coincidental onset of MS. The brain biopsy was consistent with an autoimmune response showing demyelinated foci infiltrated peripherally by T cells, similar to MS plaques [5]. 5-FU has been implicated in reversible ataxia and encephalopathy; unfortunately, observations were reported before the CT and MRI era and no pathological results are available in humans [1, 3].


Table 1  Multifocal inflammatory leukoencephalopathy associated with 5-FU and levamisole chemotherapy; summary of reports

<table>
<thead>
<tr>
<th>Study</th>
<th>First-line chemotherapy</th>
<th>Onset</th>
<th>Duration</th>
<th>Clinical signs</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fassas et al. [4]</td>
<td>5-FU</td>
<td>6</td>
<td>11-27</td>
<td>headache, vertigo, ataxia, memory loss, dysesthesia</td>
<td>multiple supratentorial with and without enhancement</td>
</tr>
<tr>
<td>Ferroir et al. [5]</td>
<td>levamisole</td>
<td>7</td>
<td>2</td>
<td>confusion, ataxia, vertigo, Babinski</td>
<td>multiple supratentorial with and without enhancement</td>
</tr>
<tr>
<td>Chen et al. [3]</td>
<td>levamisole</td>
<td>8</td>
<td>2-7</td>
<td>abnormal behavior, ataxia, aphasia, motor signs, seizures, coma</td>
<td>multiple supratentorial with and without enhancement</td>
</tr>
</tbody>
</table>

5-FU and levamisole therapy: summary of reports

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Duration</th>
<th>Clinical signs</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hook et al. [1]</td>
<td>no treatment, chemotherapy continued</td>
<td>2-7</td>
<td>multiple supratentorial with and without enhancement</td>
<td>no treatment, chemotherapy continued</td>
</tr>
<tr>
<td>Kimmel et al. [7]</td>
<td>spontaneous remission</td>
<td>2-7</td>
<td>multiple supratentorial with and without enhancement</td>
<td>spontaneous remission</td>
</tr>
<tr>
<td>Present study</td>
<td>partial</td>
<td>2-7</td>
<td>multiple supratentorial with and without enhancement</td>
<td>partial</td>
</tr>
</tbody>
</table>

Treated with levamisole alone.

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Short Reports

245 diagnosis; however, the T4-cell count was normal and the PCR analysis for JCV-DNA was negative. Short-term dexamethasone treatment and cessation of chemotherapy were beneficial. A primary CNS lymphoma was also considered because of MRI features; however, this disorder, often multisystemic, is characterized by acute or subacute evolution. In our cases, acute symptoms were transient without clinical progression; case 1 is alive almost 2 years after her illness. Hook et al. [1] gave a detailed description of 5-FU and levamisole leukoencephalopathy. Others [2–6] added evidence of a nonincidental relationship. 5-FU has been implicated in reversible ataxia and encephalopathy; unfortunately, observations were reported before the CT and MRI era and no pathological results are available in humans [1, 3]. Okeda et al. [10] proposed a toxic effect on myelin due to 5-FU and its metabolites followed by an immune response to damaged myelin due to Levamisole [4]. Reviewing the literature (table 1), unsolved problems become apparent, e.g. whether recovery was due to cessation of chemotherapy or to steroid treatment or independent of both, and why some cases recovered partially. Physicians involved in trials for cancer patients should be aware of the possible link between these drugs and demyelinating disorders.

References


11 Anonymous: Multifocal inflammatory leukoencephalopathy caused by adjuvant therapy with 5-fluorouracil and levamisole after resection for an adenocarcinoma of the colon. Acta Neurol Scand 1993;87:70.