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 (150 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 leurovin (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. 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. Ib), 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.

Fig. 1. a T2-weighted axial MRI scan (1.5 T, Signa System, TR 2500 TE 90/1) after gadolinium-DPTA: multiple, confluent enhancing lesions are seen supratentorially. b After 2-month treatment, the T2-hyperintense lesions show less enhancement than in the previous scan.
References


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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Disease duration (months)</th>
<th>Clinical presentation</th>
<th>MRI</th>
<th>Treatment</th>
<th>Type of recovery</th>
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<tbody>
<tr>
<td>Chen et al. [3]</td>
<td>2</td>
<td>Headache, vertigo, ataxia, dysarthria</td>
<td>Supra-, infratentorial with enhancement</td>
<td>Corticosteroids, cessation chemotherapy</td>
<td>Partial</td>
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<tr>
<td>Fassas et al. [4]</td>
<td>11-27</td>
<td>Confusion, ataxia, vertigo, bilateral Babinski, abnormal behavior, ataxia, aphasia, motor signs, seizures, coma</td>
<td>Multiple supratentorial with and without enhancement</td>
<td>No treatment, chemotherapy continued</td>
<td>Spontaneous remission</td>
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<tr>
<td>Kimmel et al. [7]</td>
<td>2</td>
<td>Motor weakness, dysarthria</td>
<td>Multiple supratentorial with and without enhancement</td>
<td>Corticosteroids, cessation chemotherapy</td>
<td>Partial</td>
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<td>Present study</td>
<td>7-8</td>
<td>Confusion, ataxia, vertigo, bilateral Babinski, abnormal behavior, ataxia, aphasia, motor signs, seizures, coma</td>
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<td>Corticosteroids, cessation chemotherapy</td>
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