Leukoencephalopathy Induced by Low-dose Methotrexate in a Patient with Rheumatoid Arthritis

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Abstract

We report a patient with rheumatoid arthritis (RA) who developed leukoencephalopathy while being treated with low-dose methotrexate (MTX). She suddenly developed loss of recent memory and left homonymous hemianopsia ascribable to the bilateral but right-predominant occipitotemporal lesions. Intravenous administration of dexamethasone and cessation of MTX quickly relieved her clinical symptoms. Low-dose MTX-induced leukoencephalopathy is a rare complication in RA, but is important with regard to the possibility of serious neurological sequellae.

Key words: methotrexate, rheumatoid arthritis, leukoencephalopathy

Introduction

Disease-modifying anti-rheumatic drugs (DMARDs) currently act as the main agent in the treatment of rheumatoid arthritis (RA). Among them low-dose methotrexate (MTX) is the most effective drug, which is usually used in RA patients refractory to other DMARDs and sometimes in those with a high disease activity as the first-line agent, particularly in US and European countries, although there are some risks for life-threatening adverse events, including myelosuppression and interstitial pneumonia (1-3). Mild involvement of the central nervous system (CNS), such as alteration in mood and headache, can also occur in low-dose MTX treatment, but its frequency is very low (1-4). Here, we report an RA patient who developed leukoencephalopathy shortly after starting low-dose methotrexate. The patient showed loss of recent memory and left homonymous hemianopsia, but these symptoms were quickly improved after cessation of MTX with intravenous administration of dexamethasone. We review the literature, and focus upon the clinical importance of this complication.

Case Report

A 68-year-old woman developed systemic arthralgia with no precipitating cause or significant family history. Based on persistent arthritis in multiple joints with morning stiffness in both hands she was diagnosed as having seronegative RA according to the 1987 American Rheumatism Association criteria (5) at a neighboring hospital, and was treated with prednisolone at 5 mg daily. One month later MTX at 4 mg weekly was added as a DMARD. Her arthralgia improved gradually, but 4 months after starting MTX the patient was referred to our hospital because of subacute-onset dizziness and loss of recent memory.

When she was admitted to our hospital, her body temperature and blood pressure were 37.0°C and 124/82 mmHg, respectively. Physical examination showed swelling and tenderness in the metacarpophalangeal joint of the right third finger with mildly limited mobility of bilateral knees. The disease activity score including a 28-joint count (DAS28)-CRP calculated according to the approved formula (http://www.das-score.nl/) was 1.81. No abnormal findings were detectable in either the chest or abdomen. She was slow in responding to our questions, and impairment of recent memory and left homonymous hemianopsia were seen, although...
The present patient subacutely developed loss of recent memory and left homonymous hemianopsia while being treated with low-dose MTX and prednisolone. These symptoms were ascribable to right-predominant occipitotemporal lesions shown on MRI, which involved mainly the white matter but also the cortex. High intensity signals in the apparent diffusion coefficient map of MRI with the positive enhancement effect suggested the presence of vasogenic edema and disruption of the blood-brain barrier. Bilateral but asymmetric distributions of MRI abnormalities with normocytosis in CSF are incompatible with the clinical picture of cerebrovascular disorders and encephalitis. For her CNS lesion, therefore, 2 possible causes are worth consideration. One is collagen diseases. Systemic lupus erythematosus often affecting CNS sometimes complicates RA, but the present patient manifested no symptoms or signs suggestive of the former with negative anti-nuclear antibodies in serum. The other possible cause is MTX. MRI findings in the present patient were compatible with those of MTX-induced leukoencephalopathy with regard to predominant involvement of the occipital lobe (6, 7). Rapid improvement of neurological symptoms and MRI findings after intravenous dexamethasone therapy with cessation of MTX also supports the possible central role of the latter in the pathogenesis of leukoencephalopathy in the present patient. The brain lesion as seen in the present patient also fits the reversible posterior leukoencephalopathy syndrome (RPLS) (8). Some background other than MTX, such as hypertension, renal failure and hematological malignancies, can often induce RPLS, but the present patient had no such systemic disorders (8, 9).

MTX is an inhibitor of dihydrofolate reductase, which is clinically employed as an anti-cancer drug in hematological malignancies and also as a potent immunomodulator mainly affecting lymphocytes in collagen diseases, particularly in RA (10-12). As MTX is not able to easily penetrate the blood-brain barrier (BBB) into CNS, leukoencephalopathy due to this drug has been reported to develop after either intrathecal or intravenous administrations at a high dose (8, 11). Low-dose MTX-induced leukoencephalopathy as seen in the present patient is very rare, but there are several case reports from other institutions (13-17). Clinical profiles of the 5 reported patients with low-dose MTX-induced leukoencephalopathy are summarized in Table 1. All of the patients demonstrated abnormal intensity signals mainly in the bilateral occipital lobes, and 4 of them showed visual disturbance, including hemianopsia, and/or loss of recent memory, as seen in the present patient. Despite cessation of MTX with or without additional treatment with dexamethasone 3 patients died or did not show obvious improvement of neurological symptoms (13-15), suggesting that delayed diagnosis and treatment of leukoencephalopathy might result in poor prognosis. Histopathology of the CNS in such severe cases revealed extensive demyelination and necrosis (14, 15). MTX has been reported to cause leukoencephalopathy via direct neurotoxicity or damage to the BBB (18, 19), and in the present patient vasogenic edema shown on MRI and early recovery after treatment suggest the latter as an important pathogenetic mechanism. Consider-
Figure 2. The fluid attenuated inversion recovery (FLAIR) image (a) and apparent diffusion coefficient map (c) of magnetic resonance imaging demonstrate high intensity signals in the bilateral occipitotemporal lobes but predominantly on the right side, which coincide with a decrease in cerebral blood flow on $^{131}$I-iodoamphetamine single-photon emission computed tomography (d). These lesions were slightly positive for the enhancement effect (b). One month after administration of dexamethasone the FLAIR image shows obvious improvement of abnormal high intensity signals (e).

Table 1. Clinical Profiles of the Patients with Low-dose Methotrexate-induced Leukoencephalopathy

<table>
<thead>
<tr>
<th>Author</th>
<th>Onset age/ Sex</th>
<th>Disorders treated with MTX</th>
<th>Date of MTX</th>
<th>Duration of administration</th>
<th>Interval from onset of CNS symptoms to cessation of MTX</th>
<th>Neurological symptoms</th>
<th>Localization of MRI abnormalities</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worthley and McNeil</td>
<td>53/M RA</td>
<td></td>
<td>15 mg weekly</td>
<td>3 yrs</td>
<td>3 m</td>
<td>Cognitive dysfunction</td>
<td>Bilateral occipitotemporal</td>
<td>Cessation of MTX</td>
<td>No change</td>
</tr>
<tr>
<td>Renard et al.</td>
<td>49/F Psoriatic arthritis</td>
<td>7.5 mg weekly</td>
<td>7 yrs</td>
<td>5 m</td>
<td>Visual disturbance</td>
<td>Motor disturbance of the left hand</td>
<td>Bilateral occipitotemporal</td>
<td>Cessation of MTX</td>
<td>Recovered</td>
</tr>
<tr>
<td>Yokoo et al.</td>
<td>68/F RA</td>
<td></td>
<td>4 mg weekly</td>
<td>2 yrs</td>
<td>7 d</td>
<td>Visual disturbance Gait disturbance</td>
<td>Bilateral occipital</td>
<td>Cessation of MTX</td>
<td>Died</td>
</tr>
<tr>
<td>Raghavendra et al.</td>
<td>59/F RA</td>
<td></td>
<td>7.5 mg weekly</td>
<td>5 yrs</td>
<td>1 m</td>
<td>Visual disturbance Gait disturbance Consciousness disturbance</td>
<td>Bilateral occipital</td>
<td>Cessation of MTX</td>
<td>Died</td>
</tr>
<tr>
<td>Marcon et al.</td>
<td>59/M Psoriatic arthritis</td>
<td>15 mg weekly</td>
<td>1 yr 3 m</td>
<td>ND</td>
<td>ND</td>
<td>Apraxia</td>
<td>Bilateral occipitotemporal</td>
<td>Cessation of MTX</td>
<td>Recovered</td>
</tr>
<tr>
<td>Present patient</td>
<td>68/F RA</td>
<td></td>
<td>4 mg weekly</td>
<td>4 m</td>
<td>2 m</td>
<td>Visual disturbance Cognitive dysfunction</td>
<td>Bilateral occipitotemporal</td>
<td>Cessation of MTX</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

CNS: central nervous system, MRI: magnetic resonance imaging, MTX: methotrexate, ND: not described, RA: rheumatoid arthritis

erring that leukoencephalopathy in the present patient developed with slight increases in IgG and its index in CSF only 2 months after starting MTX at 4 mg weekly, which was a relatively low dose, inflammation due to hypersensitivity to this drug might have been relevant to development of disruption of the BBB. We plan to use other DMARDs in the present patient if RA worsens again in the near future.

In conclusion, MTX-induced leukoencephalopathy can occur even with low-dose administration. This complication is rare but important as there is the possibility of neurological sequelae or death in the case of delayed diagnosis and treatment. Neurological examination and MRI are necessary.
if RA patients treated with MTX complain of symptoms or signs suggestive of CNS involvement.

The authors state that they have no Conflict of Interest (COI).

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References

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