CASE REPORT

Diffusion-weighted imaging characteristics of methotrexate-induced acute encephalopathy

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Key Clinical Message
Methotrexate (MTX)-induced encephalopathy is a grave complication in patients with malignancies. The early diagnosis of acute encephalopathy was difficult by conventional computed tomography (CT), and T1- or T2-weighted magnet resonance (MR) imaging. We report that the diffusion-weighted (DW) imaging is useful for early detection of acute leukoencephalopathy.

Keywords
Diffusion-weighted imaging, encephalopathy, magnetic resonance imaging, methotrexate, neurotoxicity.

Introduction
The computed tomography (CT)/magnetic resonance (MR) image-based diagnosis of chronic irreversible leukoencephalopathy related to methotrexate (MTX) administration has been established. This disorder is known as a complication [1].

On the other hand, acute reversible leukoencephalopathy has not been widely recognized. Recent studies indicated the usefulness of diffusion-weighted MR images for the early diagnosis of acute leukoencephalopathy [2–4].

In this study, we report a patient who developed neuropathy through a rapid course after MTX administration and was diagnosed with acute leukoencephalopathy based on diffusion-weighted MR images, leading to a favorable course by the prompt discontinuation of MTX administration.

Case Report
A 53-year-old man was diagnosed as having lymphomatoid granulomatosis involving the central nervous system (CNS) and left lower lung. Because the CNS lesions worsened, the patient underwent treatments with rituximab (375 mg/m²), MTX (3.5 g/m²), procarbazine (100 mg/m²/d/7 days), and vincristine (1.4 mg/m²) (R-MPV therapy). Leucovorin rescue was given after high-dose MTX, with no delay of MTX excretion in any course. Intrathecal injections of MTX, cytarabine, and prednisolone were given three times as part of the R-MPV therapy. No complications, such as headache, neck stiffness, or vomiting, were observed. Eleven days after the third course of R-MPV therapy, sudden dysarthria occurred around noon, and rapidly deteriorating neurological symptoms, such as paralysis of the left side of the body were noted in the right periventricular area and corona radiata on diffusion-weighted (DW) imaging, and MTX-induced acute leukoencephalopathy was
suspected. Neurological manifestations rapidly developed and were severe, but had mostly improved the following day. Cerebrospinal fluid (CSF) was examined, but was nonspecific (13 white blood and 0 red blood cells, protein 37 mg/dL, glucose 59 mg/dL, absent atypical malignant cells), and sterile without microorganisms including viruses.

High intensities on DW noted mainly in the right ventricle on day 12 (Fig. 1A) had disappeared on day 22 (Fig. 1B), but a similar high-intensity region was present in the left ventricular white matter, in addition to that in the right periventricular area, on T2-weighted and FLAIR imaging (Fig. 1B).

We initially planned to perform radiotherapy (23.4 or 45 Gy) after 5–7 cycles of R-MPV therapy, but this was suspended after three cycles because of complication by acute leukoencephalopathy. However, insufficiency of treatment of the CNS lesions was a concern. Therefore, after obtaining informed consent, application of whole-brain irradiation (45 Gy) was performed.

Five years after the complication of acute leukoencephalopathy, leukoencephalopathy has not recurred, with no signs of recurrence of CNS lesions of lymphoma.

**Discussion**

Representative drugs that cause drug-induced leukoencephalopathy include MTX as a folic acid antagonist, which inhibits folic acid reductase, dihydrofolate reductase. MTX inhibits DNA synthesis and is used for cancer treatment [5–7].

Methotrexate does not pass through the blood–brain barrier, and administration at a standard dose may not cause disorder of the nervous system. However, when selecting this drug to prevent/treat the central nervous system infiltration of tumors, it may cause neuropathy,
such as leukoencephalopathy, due to high-dose administration.

The incidence of MTX-associated leukoencephalopathy is reportedly ≤10% when MTX alone is intravenously administered [8]. However, it increases to approximately 40% when MTX is administered to elderly patients, when it is directly administered into the pulp cavity, or when MTX therapy is combined with radiotherapy. In such cases, the risk of central nervous system disorders is high [3, 9, 10].

As the mode of onset, acute to subacute/chronic leukoencephalopathy may occur. In particular, acute leukoencephalopathy has recently been investigated, and the incidence of acute leukoencephalopathy after MTX administration to cancer patients was 3% to 15% [11–13].

With respect to the diagnosis of MTX-associated leukoencephalopathy, it has been impossible to detect abnormalities in the early stage, based on CT, T1-/T2-weighted MR, or FLAIR images. However, recently, the usefulness of diffusion-weighted MR images has been emphasized. The results of several case reports regarding MRI findings of acute leukoencephalopathy are summarized in Table 1 [14, 15]. On MR images in patients with leukoencephalopathy, a focus localized in the white matter around the lateral ventricle was visualized in the initial phase and progressed to bilateral symmetric diffuse foci. Severe cases exhibit the findings suggestive of necrotic foci. In particular, patients with MTX-induced encephalopathy tend to show multiple necrotic foci. Concerning signal ranges related to MRI methods, a localized, high-signal intensity was detected on DWI in most cases even in the initial phase, as shown in Table 1, and a symmetric high-signal-intensity focus was visualized in the white matter around the lateral ventricle on T2-weighted and FLAIR images. Furthermore, in the initial phase, a low-signal intensity was detected on ADC. A study indicated that a high-signal intensity on DWI in the initial phase was useful for differentiating MTX-induced encephalopathy from reversible posterior leukoencephalopathy syndrome (RPLS), which shows a low-signal intensity [2–4].

Concerning the treatment for MTX-associated leukoencephalopathy, it is recommended that MTX administration should be promptly discontinued as a basic strategy. Although a consensus regarding this has not been reached, some studies suggested the usefulness of leucovorin or aminophylline administration for prevention/treatment [6]. Leucovorin is a folic acid metabolism antagonist that promotes MTX excretion [16]. Aminophylline substitutes adenosine, which is considered to be an etiological factor for acute leukoencephalopathy [17].

In addition, we review the clinical course of leukoencephalopathy with respect to the different modes of onset described above. Acute MTX-associated leukoencephalopathy develops 5 to 14 days after MTX administration, but subsided within 1 week after the discontinuation of MTX administration in many cases. However, a study reported that recurrence was noted in 10% to 56% of patients after the resumption of MTX administration or radiotherapy. Thus, therapeutic strategies must often be reviewed. Furthermore, chronic leukoencephalopathy slowly progresses in a few months, leading to an irreversible condition [11–13].

Based on these findings, we propose that mild psychiatric/neurological symptoms should be carefully followed up in MTX-treated patients and that the assessment of diffusion-weighted MR images should be promptly performed in the presence of abnormalities for the early diagnosis of acute leukoencephalopathy.

**Authorship**

MY: supervised the evaluation of the management of the patient as well as wrote the manuscript in its entirety; SA: contributed to diagnostic imaging, especially evaluation of MRI images.

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| Report     | Age (years)/Sex | FLAIR/T2WI (day 0) → DWI (day 0) |
|------------|----------------|----------------------------------|
| Mayumi Y   | 53/M           | Negative → Hyperintense (day 22)  | Localized, increased |
| Jiwon Yang | 19/M           | Negative                         | Restricted          |
| H. Inaba   | 12/M           | Hyperintense (day 0)             | Restricted          |
| H. Inaba   | 16/M           | Negative → Hyperintense (day 4)   | Restricted          |
| H. Inaba   | 14/F           | Near normal (day 4)              | Restricted          |
| H. Inaba   | 18/M           | Negative → Hyperintense (day 3)   | Restricted          |
| H. Inaba   | 7/F            | Negative → Hyperintense (day 5)   | Increased           |
| H. Inaba   | 14/F           | Negative → Hyperintense (day 2)   | Restricted          |
| H. Inaba   | 14/M           | Negative → Hyperintense (day 2)   | Restricted          |
| H. Inaba   | 18/F           | Negative → Hyperintense (day 3)   | Restricted          |

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Conflict of Interest

None declared.

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