**Letter to the editor**

Methotrexate (MTX) is a folic acid antagonist that prevents cell replication by disrupting DNA, RNA, thymidylate, and protein synthesis through the inhibition of dihydrofolate reductase. Its capacity to cross the blood-brain barrier and eliminate leukemic cells from the central nervous system makes MTX a critical component in the treatment of acute lymphoblastic leukemia (ALL) [1-3]. However, MTX can also cause adverse effects such as neurotoxicity, myelosuppression, mucositis, liver damage, and kidney failure [2,3].

Patients with leukemia may exhibit focal neurological deficits due to various conditions, including cerebral infarction, intracranial hemorrhage, and infection. MTX-induced neurotoxicity can present with stroke-like symptoms, which may be difficult to distinguish from those of an actual stroke [4,5]. We report a case of MTX-induced stroke-like leukoencephalopathy in a patient with ALL who experienced complete neurological recovery. This study received approval from the Institutional Review Board of Daegu Catholic University Medical Center (CR-24-005). The requirement for obtaining publication consent was waived, as this report contains no personally identifiable protected health information.

An 18-year-old man with ALL was admitted for delayed intensification chemotherapy. Five days after receiving intrathecal (IT) triple therapy (MTX 15 mg, cytarabine 30 mg, and hydrocortisone 15 mg), he developed weakness in his right arm. Within the next 18 hours, his motor weakness worsened; he also began to exhibit slurred speech, which evolved into motor aphasia and dysphagia. The patient’s Medical Research Council grades for motor power were grade 3 for the right arm and grade 4 for the right leg. His vital signs were as follows: heart rate 120 beats/min (normal range, 55 to 85), respiratory rate 22 breaths/min (normal range, 12 to 18), body temperature 36.8°C (normal range, 36.5°C to 37.4°C), and blood pressure 130/80 mm Hg (normal range, 110–135/65–85). Laboratory findings included hemoglobin, 7.4 g/dL; white blood cells, 300/μL (with 195 neutrophils/μL); platelets, 40,000/μL; prothrombin time, 14 seconds (normal range, 10.0 to 13.5); partial thromboplastin time, 14 seconds (normal range, 10.0 to 13.5); fibrinogen, 552 mg/dL (normal range, 180 to 400); antithrombin III, 120.7% (normal range, 80% to 120%); and D-dimer, 1.3 μg/mL (normal range, 0 to 0.55). Emergent brain magnetic resonance imaging (MRI) revealed a patchy area of hyperintensity on diffusion-weighted imaging (DWI) in the left frontoparietal subcortical and deep white matter, with a corresponding hypointense signal on the apparent diffusion coefficient map. Fluid-attenuated inversion recovery (FLAIR) images showed no abnormalities (Fig. 1A-D). Three-dimensional (3D) computed tomography (CT) of the cerebral arteries yielded normal results. After excluding stroke due to vascular infarction or other potential causes, MTX-induced toxic leukoencephalopathy was diagnosed.
No specific treatment was administered, and the patient gradually improved with physical therapy. Eight days after the onset of symptoms, he had almost fully recovered. On day 12, only follow-up DWI MRI was performed, as restricted diffusion was the sole abnormal finding on the initial MRI. The follow-up MRI revealed resolution of the lesion in the left frontoparietal white matter (Fig. 1E and F). Two months later, the patient received further IT and intravenous (IV) MTX. Despite the reintroduction of MTX, he experienced no further episodes of stroke-like leukoencephalopathy. Five months after the initial presentation, repeated MRI displayed patchy hyperintensities in the right frontal and left frontoparietal white matter on FLAIR imaging, but these findings were not associated with clinical symptoms (Fig. 1G and H).

Stroke-like leukoencephalopathy is a specific form of subacute neurotoxicity that manifests days to weeks after MTX administration. High doses of MTX and an age over 10 years are associated with a higher risk of neurotoxic events [6]. Clinical features include a sudden onset of focal neurological deficits such as hemiparesis, sensory deficits, aphasia, dysarthria, dysphagia, altered mental status, and occasionally seizures. These symptoms resolve spontaneously in most cases [6,7]. Unlike in ischemic stroke, the MRI findings characteristically show transient restricted diffusion in the subcortical and periventricular white matter, especially in the centrum semiovale, without initial FLAIR signal abnormalities. The areas of diffusion restriction extend beyond the confines of the vascular territories. In almost all previously reported cases, follow-up MRI indicated resolution of the restricted diffusion [3,4,7-10]. Notably, one case report described confluent FLAIR hyperintensities in the periventricular white matter without evidence of restricted diffusion, indicating that diffusion restriction may not always be present during the acute phase of the disease and that T2/FLAIR hyperintensities can represent the sole abnormalities [10]. Watanabe et al. [5] reported that a normal coagulation profile is typical of MTX-induced stroke-like neurotoxicity, in contrast to cerebral infarction, which is often accompanied by elevated levels of fibrin degradation products and D-dimer. While the mechanism of this syndrome is not fully understood, it is likely multifactorial. The normal coagulation profile and lesion distribution beyond vascular...
territories suggest that a vasculopathic explanation is improbable [8]. Proposed mechanisms for MTX neurotoxicity include direct toxicity of homocysteine and its metabolites on the vascular endothelium and their excitatory effects on N-methyl-D-aspartate receptors, increased adenosine release contributing to neurotoxicity and white matter injury, chronic folate depletion in brain tissue, and direct neuronal damage by MTX [1,4,6,7]. The management of MTX-induced stroke-like leukoencephalopathy is primarily supportive. However, in some patients, treatments such as additional folic acid, leucovorin rescue, dexamethasone, aminophylline, and dextromethorphan have been used [1,4,9]. This syndrome is usually transient, and patients can achieve complete neurological recovery; however, chronic radiographic sequelae may persist, as observed in the present case [2,8,9]. For the patient in this case, follow-up MRI conducted at 5 months revealed patchy hyperintensity in the right frontal white matter, which did not correspond to the initial diffusion abnormality. Previous case reports have shown a poor correlation between white matter lesions and clinical neurological deficits. MTX neurotoxicity has presented without radiologic correlates, while leukoencephalopathy has developed in asymptomatic patients with ALL. Moreover, T2/FLAIR hyperintensities on follow-up MRI have not consistently matched the areas of white matter previously abnormal on DWI. White matter lesions on conventional MRI are known to be temporary and reversible in some patients; however, as seen in our patient, progressive and persistent white matter changes can occur without symptomatic neurotoxicity [5,8,9]. Dharwal et al. [9] examined the radiological profile of MTX-induced neurotoxicity in 33 patients and found that, in cases for which follow-up imaging was available, patients remained stable even as MRI findings progressed. Although MTX re-exposure can induce relapses, such events are reported to be rare, and those affected generally experience a full recovery. Therefore, a history of this event should not necessarily preclude further MTX use, considering the outcomes [5,9]. The patient in this case report received two additional administrations of MTX via the IT/IV route and experienced no further episodes of MTX-related neurotoxicity. When he developed focal neurological deficits with diffusion restriction on brain MRI, the initial presumptive diagnosis was ischemic stroke. Before normal results were obtained for a 3D CT scan of the cerebral arteries, stroke management was considered for this patient. However, with blood tests indicating thrombocytopenia and a normal coagulation profile, an alternative diagnosis was required for further evaluation and management. Had we been familiar with MTX neurotoxicity from the outset, we could have identified this condition as the most likely diagnosis. As MTX is a cornerstone drug in the treatment of ALL, clinicians should be aware of this stroke-like leukoencephalopathy to avoid unnecessary diagnostic procedures and treatments.

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

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**Author contribution**

Conceptualization: NWL and KHL. Data curation: NWL and KHL. Formal analysis: NWL and KHL. Methodology: NWL and KHL. Project administration: NWL and KHL. Visualization: NWL and KHL. Writing - original draft: NWL. Writing - review & editing: KHL.

**References**

