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LETTER TO THE EDITOR

Methotrexate-induced toxic leukoencephalopathy: an uncommon stroke mimic

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Dear Sir,

Focal neurologic deficits in immunocompromised leukemia patients can be caused by a variety of conditions, among them central nervous system (CNS) involvement, cerebral infarction, intracranial hemorrhage, and (opportunistic) infections [1]. We here describe a young woman with acute leukemia who presented with a stroke-like syndrome due to toxic methotrexate-induced leukoencephalopathy. As methotrexate is commonly administered intrathecally, clinicians should be aware of this rare side effect. Timely recognition of the typical MRI abnormalities can prevent unnecessary diagnostic procedures and has implications for treatment and prognosis.

A 19-year-old woman was admitted to the emergency department because of dysarthria and uncoordinated gait that had commenced the evening before presentation. She also reported numbness and paresthesias in the left arm and difficulty dressing herself due to left hand weakness. There was no headache, nausea, vomiting, diplopia, or reduced visual acuity. Seventy days before admission, she underwent an allogeneic stem cell transplantation because of relapsed acute undifferentiated leukemia and was started on cyclosporine as graft-versus-host disease prophylaxis. CNS-directed prophylactic chemotherapy with intrathecal methotrexate was administered 40 days and 12 days prior to admission, and a third lumbar puncture had been scheduled. Neurologic examination revealed mild central facial palsy, hemihypesthesia, slight pyramidal weakness, and hyperreflexia, all on the left side. Examination of mental status was normal and there was no nuchal rigidity or fever. Brain MRI showed an area of hyperintensity on diffusion-weighted sequences in the right centrum semiovale and in the splenium of the corpus callosum with a corresponding hypointense signal on the apparent diffusion coefficient map (Fig. 1). A less prominent hyperintense signal in the aforementioned areas was also visible on T2-weighted images. There was no contrast enhancement. Cerebrospinal fluid (CSF) contained 2 leukocytes/μl, 0 erythrocytes/μl, a protein content of 34.5 mg/dl, a glucose concentration of 2.9 mmol/l, and a CSF/serum glucose ratio of 0.54. Bacterial or fungal growth could not be demonstrated and tests for JC virus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus 1 and 2, varicella zoster virus, and enterovirus, and cryptococcal antigen returned negative. Flow cytometric immunophenotyping provided no evidence of CNS involvement. The following day, the patient's symptoms had disappeared completely. Given the transient nature of neurologic deficits, occurrence within 2 weeks after intrathecal methotrexate administration, typical diffusion-weighted imaging abnormalities in the centrum semiovale and splenium of the corpus callosum, and unremarkable CSF results, a diagnosis of toxic methotrexate-induced leukoencephalopathy with stroke-like presentation was established. A follow-up MRI scan 7 weeks after admission revealed residual T2 hyperintensities in the splenium and right centrum semiovale, albeit less prominent than before. Diffusion restriction was no longer present. Based on this diagnosis, the third and last administration of intrathecal methotrexate was canceled.

Methotrexate is a frequently administered antineoplastic agent in both the prophylaxis and treatment of CNS involvement in acute lymphoblastic leukemia (ALL). It works as a dihydrofolate reductase inhibitor, thus preventing the conversion of dihydrofolate to tetrahydrofolate and increasing concentrations of homocysteine. Although the precise underlying

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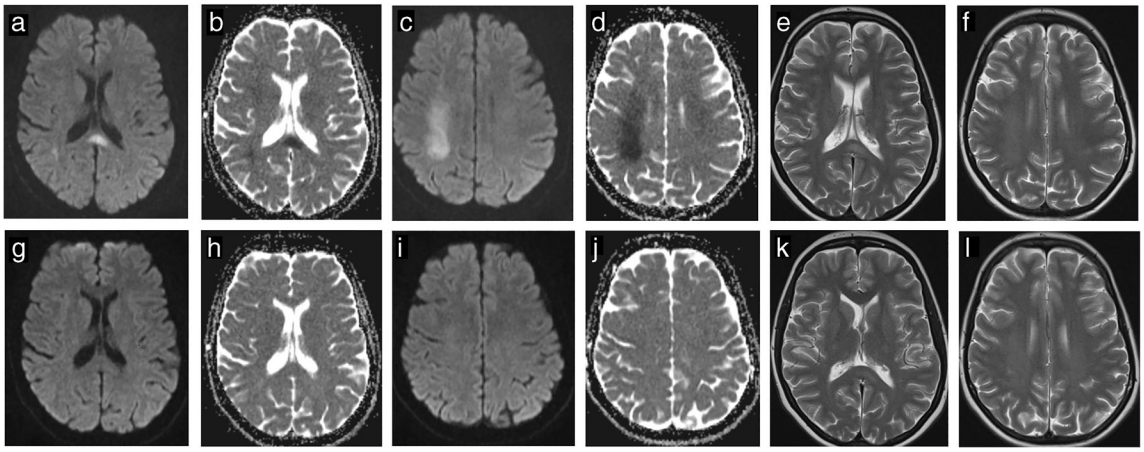

Fig. 1 MRI abnormalities in a 19-year-old acute leukemia patient with methotrexate-associated leukoencephalopathy and stroke-like presentation. Diffusion-weighted imaging (A, C, G, I), apparent diffusion coefficient maps (B, D, H, J), and T2-weighted sequences (E, F, K, L) at admission (upper row) and after 7 weeks of follow-up (bottom row). Initially, hyperintense signals were observed in the splenium of the corpus callosum and right centrum semiovale on diffusion-weighted imaging and T2-weighted sequences along with hypointense signals on the corresponding apparent diffusion coefficient maps. Follow-up MRI after 7 weeks showed less conspicuous T2 hyperintensities in these areas and, to a lesser extent, in the left centrum semiovale, while diffusion restriction was no longer present

pathophysiological mechanism of acute methotrexate-induced leukoencephalopathy with stroke-like presentation remains to be elucidated, the observed intramyelinic sheath edema has been hypothesized to result from a transient metabolic encephalopathy rather than from a vascular etiology [2]. Homocysteine and its metabolites, well-known for their excitatory effects on N-methyl-D-aspartate (NMDA) receptors and toxicity to the cerebrovascular endothelium, and adenosine most likely play a pivotal role, presumably superimposed on a specific genetic background [3–7]. Levels of CSF homocysteine and its excitotoxic metabolites were found to be significantly elevated in children who were just treated with intravenous methotrexate as compared to patients without exposure to this drug [3]. In addition, increased CSF adenosine concentrations were demonstrated after administration of methotrexate [4, 5]. The subsequent binding of this ribonucleoside to the adenosine A2A receptor may enhance the release of excitatory neurotransmitters, further contributing to neurotoxicity and white matter injury. Interestingly, a polymorphism in the gene encoding the adenosine A2A receptor was associated with methotrexate-induced leukoencephalopathy [6]. Furthermore, data from another study indicate that polymorphisms in genes involved in neurogenesis render children with hematological malignancies more susceptible to the development of neurotoxic side effects of methotrexate [7].

Late-onset neurotoxicity manifesting as progressive cognitive deterioration, gait disturbance, and urinary incontinence is a well-established long-term sequela of methotrexate infusion in primary CNS lymphoma and occurs most often after months to years, especially when patients have also been treated with whole brain radiotherapy [8, 9]. An acute or subacute onset of symptoms with headache, confusion, disturbed consciousness, seizures, and/or stroke-like presentation including focal neurologic deficits has been described in 14 of 369 ALL patients (3.8%) treated with this drug, more commonly in patients above 10 years of age and those receiving higher doses [7]. A review of the literature published in 2008 identified only 18 cases with stroke-like presentation after intrathecal methotrexate administration and one after systemic infusion, all but one occurring in ALL patients [2]. The age of these patients ranged from 13 to 20 years, symptoms started 6 h to 11 days after infusion, and completely subsided in all cases after several hours to 1 month. In a very recently published case series, Watanabe and colleagues compared the characteristics of pediatric leukemia or lymphoma patients with methotrexate-induced stroke-like neurotoxicity on the one hand and those with cerebral infarction and venous sinus thrombosis on the other and found distinctively normal coagulation tests in the former group. All four children with stroke-like presentation presented in the early intensification phase 10 to 13 days after the fourth or fifth intrathecal methotrexate administration and showed resolution of symptoms within 5 days [10].

Lesions in patients with leukoencephalopathy and stroke-like presentation are typically characterized on MRI by diminished water diffusion and are most commonly distributed bilaterally in the centrum semiovale with sparing of the cortex [10–12]. Unilateral abnormalities and involvement of the splenium of the corpus callosum have also been described [2, 13]. Though suggestive, it should be noted that diffusion restriction is not necessarily present during the acute phase of the disease and T2 and FLAIR hyperintensities can be the only abnormalities [14].

As symptoms typically resolve spontaneously, recognition of the quintessential clinicoradiologic syndrome is crucial to avoid unnecessary invasive examinations and refrain from

administration of intravenous thrombolysis and initiation of secondary stroke prevention drugs. In addition to leucovorin (folinic acid), some authors advocate the use of aminophylline, a nonselective adenosine receptor antagonist, and dextromethorphan, which acts as an NMDA receptor antagonist [5, 14–16]. However, others are more skeptical on this point [2]. Re-introduction of methotrexate can induce relapses, but this has been reported in only 1 out of 13 patients and 1 out of 4 patients in two recent series [7, 10]. A history of leukoencephalopathy with stroke-like presentation should therefore not be considered an absolute contraindication for re-exposure, but decisions on further methotrexate management probably ought to be made on a case-by-case basis.

Compliance with ethical standards

Conflict of interest Roderick Maas, Sjoert Pegge, Dorothea Evers, and Anusha van Samkar report no disclosures.

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Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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