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METHOTREXATE – INDUCED LEUKOENCEPHALOPATHY
A Case Report*

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SUMMARY: İlhan İ, Cila A, Büyükpamukçu M, Akyüz C, Kutluk T, Berberoğlu S. (Oncology Unit, Department of Pediatrics, and the Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey). Methotrexate-induced leukoencephalopathy: a case report. Turk J Pediatr 1995; 37: 275-278.

A six-year-old girl with non-Hodgkin's lymphoma who was treated with both intravenous (IV) and intrathecal (IT) methotrexate and developed brain damage secondary to the cytostatic drug is described. This patient displayed hypertension, hypothermia/ hyperthermia, lethargy, deterioration and coma as clinical findings, and bilateral, focal white matter hyperintensities in the occipital lobes were seen in her magnetic resonance imaging (MRI). Treatment-related leukoencephalopathy is one such adverse effect of IT methotrexate administration on the central nervous system and usually appears in a generalized form. *Key words: leukoencephalopathy, intrathecal methotrexate, non-Hodgkin's lymphoma.*

Methotrexate (MTX) is one of the most commonly used cytostatic drugs in both children and adults with malignant disease[1,2]. Methotrexate can be given intrathecally (IT) either for therapeutic or prophylactic purposes, but it can cause several central nervous system (CNS) complications which can be difficult to differentiate from the original disease.

The aim of this study was to present a case of focal leukoencephalopathy developed due to IT methotrexate administration, as leukoencephalopathy is usually seen in a generalized form.

Case Report

A six-year-old girl was admitted to Hacettepe Children's Hospital with an abdominal mass and right-sided pleural effusion. A diagnosis of non-Hodgkin's

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lymphoma was made on the basis of cytological findings from pleural effusion. Bone marrow aspiration was normal. She was in stage III according to Murphy's staging system[3]. She was given chemotherapy with the BFM-B cell NHL protocol[4]. After six courses of chemotherapy she had only a 20 x 15 mm lymphadenopathy in front of the pancreas, as detected by ultrasonography. After the COMP protocol[5] was started, she developed dysuria, constipation, cramps and weakness in both legs within two days of her last intravenous (IV, 500 mg/m^2) and IT MTX (12 mg/m^2) administration. A chest wall mass and hilar lymphadenopathy displayed L3-type blastic infiltration. Hypertension and hypothermia-hyperthermia attacks were followed by lethargy, generalized convulsions and deterioration of consciousness. The cerebrospinal fluid (CSF) pressure was 18 cm H_20, with a protein content of 39 mg/dl. Cerebrospinal fluid virus cultures and serum antibody tests were all negative. Electroencephalography (EEG) was within normal limits. Computerized tomography (CT) showed minimal brain atrophy (Fig. 1). High-dose methylprednisolone (30 mg/kg/day) administration was started. One week later magnetic resonance imaging (MRI) revealed bilateral, asymmetric, occipital, white matter hyperintensities which extended into the U-fibers. T1-weighted images showed the lesion only on the right side, which was hypointense relative to the white matter, and no enhancement occurred after Gd-DTPA infusion (Fig. 2).

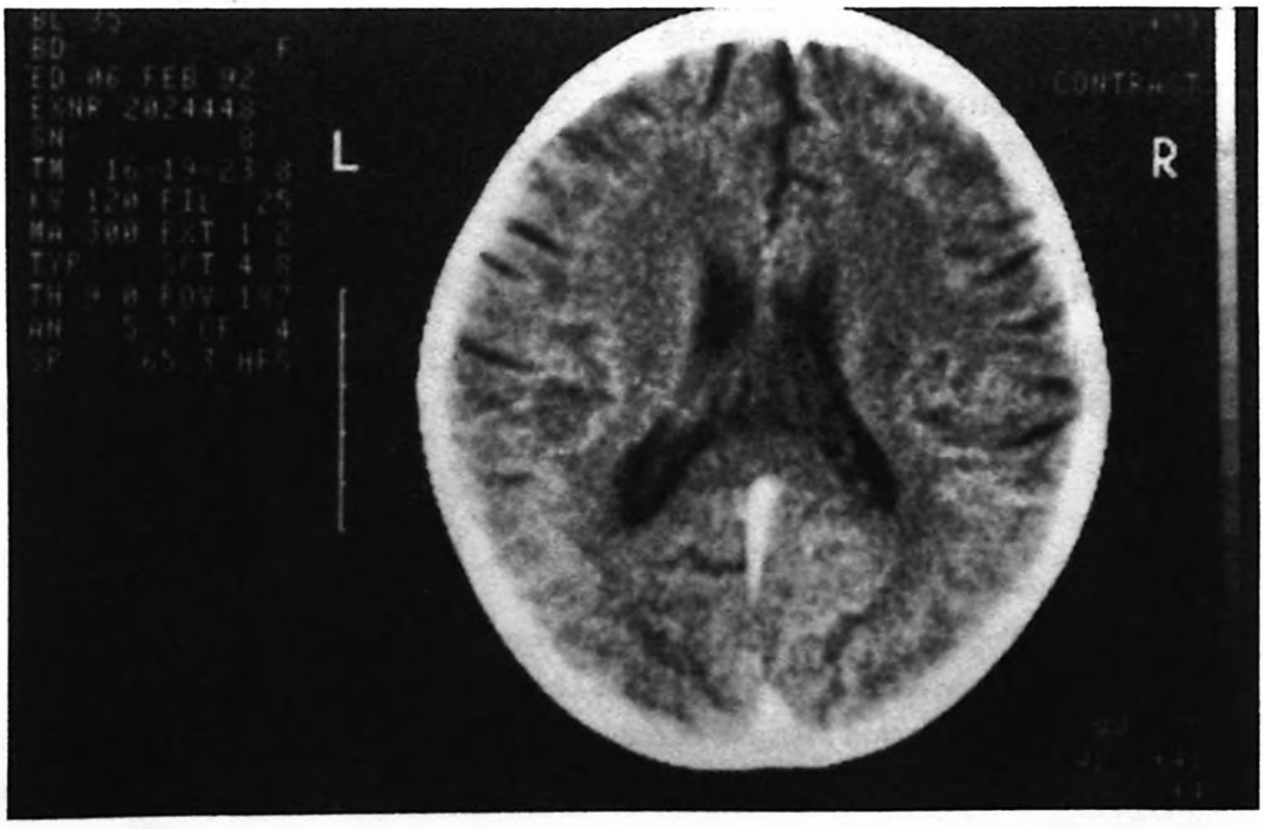

Fig. 1: CT scan. The white matter density is normal in both of the occipital lobes.

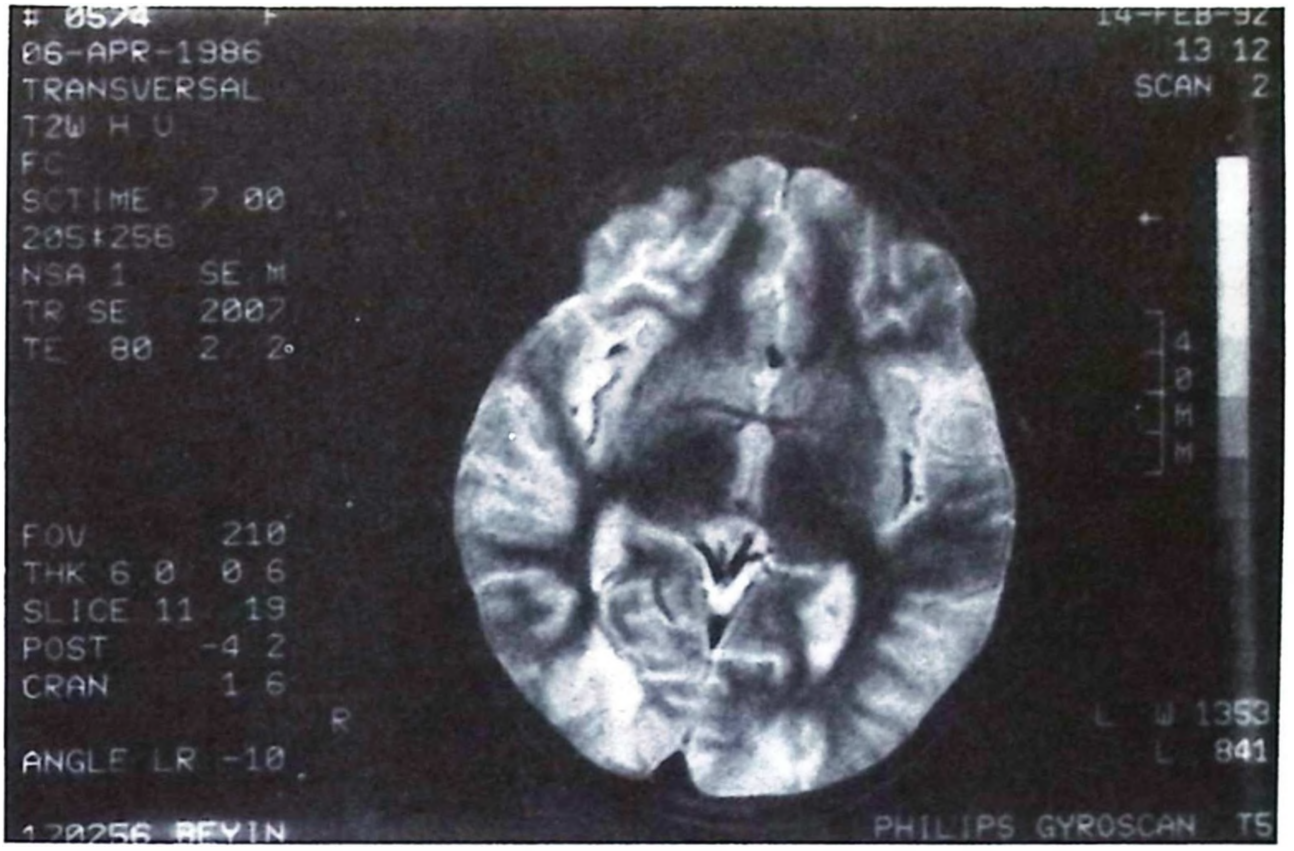

Fig. 2: MRI performed one week later shows bilateral white matter hyperintensities in the occipital lobes extending into the U-fibers.

Two days later, the patient developed a maculo-vesicular rash which was later diagnosed as varicella. Bone marrow aspiration as positive for L3-type blastic infiltration for the first time during the course of her disease. Although acyclovir treatment was started, she died on the third day of her varicella infection.

Discussion

Treatment-related leukoencephalopathy is defined as an entity in which acute or delayed changes in white matter secondary to chemotherapy and/or radiotherapy produce CNS dysfunction[6]. Necrotizing encephalopathy and subacute leukoencephalopathy are terms used to define the same pathology[7]. The chemotherapeutic agents most commonly implicated in its pathogenesis are MTX, Ara-C, BCNU, cisplatin and thio-TEPA. High-dose IV (8-20 g/m^2) and IT/intraventricular injection of MTX is a common cause of leukoencephalopathy[1,8]. Our patient received 12 mg MTX at each IT administration (total 84 mg), and her total IV dose was 3000 mg.

Neurologic symptoms may appear during the treatment (acute), within a few weeks to months after the treatment (early delayed) or several years later (late delayed)[7]. The disease must be distinguished by specific laboratory tests from several other clinical entities such as tumoral infiltration, infection, toxic-metabolic encephalopathy, disseminated intravascular coagulopathy, arteritis and

progressive multifocal encephalopathy. Computerized tomography may show diffuse, white matter hypodensity[9]. Biti et al.[10] reported that MRI showed an abnormal focus in all patients with normal CT findings. We performed imaging studies such as CT, MRI, biochemical and viral studies to establish the etiology of encephalopathy and concluded that it may be treatment-related acute-type leukoencephalopathy. Our patient's CT showed no focal lesion, while the MRI demonstrated abnormal white matter changes. Although there are some reports of generalized leukoencephalopathy due to IT MTX administration, our report is important because her MRI showed focal leukoencephalopathic changes[1, 4, 7]. Since our patient received both IV and IT MTX, it is difficult to distinguish whether the leukoencephalopathy was related to one or both. High-dose steroids and folinic acid is the treatment of choice, but it may be complicated by a superimposing infection, such as varicella in our patient.

In summary, IT MTX administration has been useful in prophylactic treatment of leukemia and lymphoma, but it may cause neurotoxicity as well. Serious and life-threatening forms are rare; thus the effectiveness of prophylactic therapy outweighs the risks.

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