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Methotrexate-Mediated Arachnoiditis in a Child with Acute Lymphoblastic Leukemia

Akut Lenfoblastik Lösemili bir Çocukta Gelişen Metotreksat İlişkili Araknoidit

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To the Editor,

A 3-year-old girl was diagnosed with precursor B-cell acute lymphoblastic leukemia (B-ALL) and treatment was started according to the ALL-BFM-2000 protocol. She was classified as standard risk with steroid responsivity on day 8 and had complete remission on day 33 without any cytogenetic abnormalities. Consolidation treatment with the first three high doses of methotrexate (MTX; 5 g/m^2) as per the protocol was implemented without a problem. However, at the last high dose of MTX (HDMTX), cerebrospinal fluid (CSF) examination showed abundant cells. Biochemical analysis of the CSF revealed markedly increased protein (344 mg/dL; normal: 15-45 mg/dL) and a decreased glucose level (43 mg/dL, plasma glucose 92 mg/dL). Cytospin morphologic examination of the CSF showed many mononuclear cells (Figures 1A and 1B). Both neurologic and ophthalmologic examinations and cranial magnetic resonance imaging (MRI) results were normal. Genetic polymorphisms of *MTHFR* (c.677C>T; c.1298 A>C) were analyzed and the heterozygous variant of C677T was identified. Bone marrow examination showed complete remission. As CSF leukemic involvement could not be ruled out, CSF analysis was repeated twice weekly with triple intrathecal treatment (TIT) (MTX, cytarabine, and steroids). The next four CSF examinations indicated the same mononuclear cells and CSF protein levels were still high. No blastic cells were identified in the CSF by flow cytometric analysis (Figure 1C). When spinal MRI showed thickened nerve roots (Figure 1D) concordant with arachnoiditis, the administration of TIT was immediately ceased. After that, as the mononuclear cells completely disappeared and protein levels returned to normal within 2 weeks (Figure 1E), the cells were attributed to MTX-mediated arachnoiditis.

High-dose systemic and intrathecal MTX can cause chemical arachnoiditis in patients with leukemia [1]. A few studies have reported that these complications generally occurred between the second and fourth doses of HDMTX in patients with leukemia. In these cases, seizures, headache, back pain, and vomiting were present but markedly elevated protein and persistent abundant mononuclear cells were not previously reported, in contrast to our case [1,2,3]. Furthermore, the mononuclear cells disappeared with the cessation of TIT. All of these findings supported the diagnosis of HDMTX-mediated arachnoiditis in our case. The polymorphic variant of C677T in the *MTHFR* gene in patients with ALL has been associated with MTX-related liver, intestinal, hematologic, and mucosal toxicities [4,5], but MTX-mediated arachnoiditis linked to the same genetic variant has not been reported before. Our experience suggests that leukemia specialists should be aware of MTX-mediated arachnoiditis in asymptomatic children with leukemia when abundant mononuclear cells are coincidentally detected in the CSF with nonspecific flow cytometry and specific imaging findings for arachnoiditis.

Keywords: Arachnoidit, Leukemia, Methotrexate

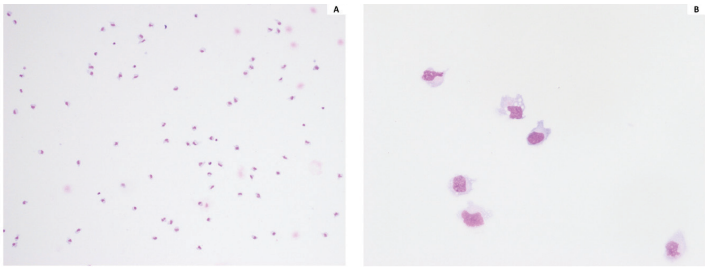
Anahtar Sözcükler: Araknoidit, Lösemi, Metotreksat

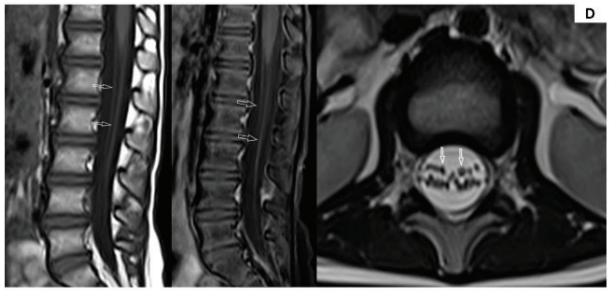
Ethics

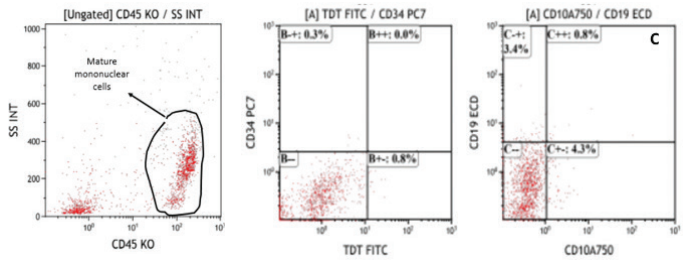
Informed Consent: Informed consent was obtained from the parents of the patient. The parents of the patient provided informed consent regarding the publication of all data and photographs.

Authorship Contributions

Concept: S.K., Z.K., P.U.G., B.T.T., M.Y., Ö.B., Ü.K.; Design: S.K., Z.K., P.U.G., B.T.T., M.Y., Ö.B., Ü.K.; Data Collection or Processing: S.K., Z.K., P.U.G., B.T.T., M.Y., Ö.B., Ü.K.; Analysis or Interpretation: S.K., Z.K., P.U.G., B.T.T., M.Y., Ö.B., Ü.K.; Literature Search: S.K., Z.K., P.U.G., B.T.T., M.Y., Ö.B., Ü.K.; Writing: S.K., Z.K., P.U.G., B.T.T., M.Y., Ö.B., Ü.K.







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ALL-BFM protocol scheme		Protein levels in CSF (mg/dL)	Cells in CSF	Intrathecal treatment
Protocol-1		41,00	-	Methotrexate
		48,00	-	Methotrexate
		56,00	-	Methotrexate
		43,00	-	Methotrexate
		25,00	-	Methotrexate
Protocol-M	HDMTX-1	33,00	-	Methotrexate
	HDMTX-2	11,00	-	Methotrexate
	HDMTX-3	29,00	-	Methotrexate
	HDMTX-4	344,00	Abundant	Methotrexate
		225,00	Abundant	Triple
		191,00	Abundant	Triple
		171,00	Abundant	Triple
		154,00	Abundant	Triple
		106,00		-
		87,00	-	-
		50,00	-	-
		23,00	-	-

HDMTX: High dose methotrexate, ALL-BFM:Acute lymphoblastic leukemia-Berlin-Frankfurt-Münster, CSF: Cerebrospinal fluid, Triple: methotrexate, cytarabine, and steroid.

Figure 1. Abundant mononuclear cells in the cerebrospinal fluid (CSF) were demonstrated by cytospinning (Wright stain, 10^x) (A); arachnoid cells in CSF cytospinning (Wright stain, 40^x) (B); flow cytometric examination (C); arachnoiditis (white arrow) revealed by magnetic resonance imaging (D); and changes in CSF protein levels and values of intrathecal treatment (E) in a child with precursor B-cell acute lymphoblastic leukemia.

Conflict of Interest: No conflict of interest was declared by the authors.

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