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Methotrexate Mediated Arachnoiditis in a Child with Acute Lymphoblastic Leukemia
Akut Lenfoblastik Lösemili Bir Çocukta Gelişen Metoteksat Ilişkili Araknoidit

Karamercan et al. Methotrexate Mediated Arachnoiditis in a Child with Acute Lymphoblastic Leukemia

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To the Editor

A three-year-old girl was diagnosed with precursor B-ALL and treatment had been started according to ALL-BFM-2000 protocol. She was classified as standard risk with steroid responsivity on Day 8 and complete remission on Day 33 besides without any cytogenetic abnormalities. Consolidation treatment with the first three high-dose MTX (HDMTX) (5 g/m2) per protocol was implemented without a problem. However, at the last dose of HDMTX, cerebrospinal fluid (CSF) examination showed abundant cells. Biochemical analysis of CSF revealed markedly increased protein (344 mg/dL) (normal: 15-45mg/dL) and a decreased glucose level (43 mg/dL, plasma glucose 92 mg/dL). Cytospin morphologic examination of CSF showed plenty of mononuclear cells (Figure 1A, 1B). Both neurologic and ophthalmologic examinations and cranial magnetic resonance imaging (MRI) were normal. Genetic polymorphisms of MTHFR (c.677C>T; c.1298 A>C) were analyzed and 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

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twice weekly with triple intrathecal treatment (TIT) (methotrexate, cytarabine, and steroid). The next four CSF examinations indicated the same mononuclear cells and CSF protein levels were still high. No blastic cells were identified in CSF by flow cytometric analysis (Figure 1C). When spinal MRI showed thickened nerve roots (Figure 1D) that is concordant with arachnoiditis, administration of TIT was immediately ceased. After that, as the mononuclear cells completely disappeared and protein levels returned to normal within two weeks (Figure 1E) the cells were attributed to methotrexate-mediated arachnoiditis.

High-dose systemic and intrathecal methotrexate can cause chemical arachnoiditis in patients with leukemia [1]. A few studies have reported that these complications generally occurred between the second and the fourth dose of HDMTX in patients with leukemia. In these cases, seizures, headache, back pain, and vomiting were present whereas markedly elevated protein and persistent abundant mononuclear cells were not previously reported in contrast to our case [1-3]. Besides 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 in CSF are coincidentally detected with nonspecific flow cytometry and specific imaging findings for arachnoiditis.

Ethics

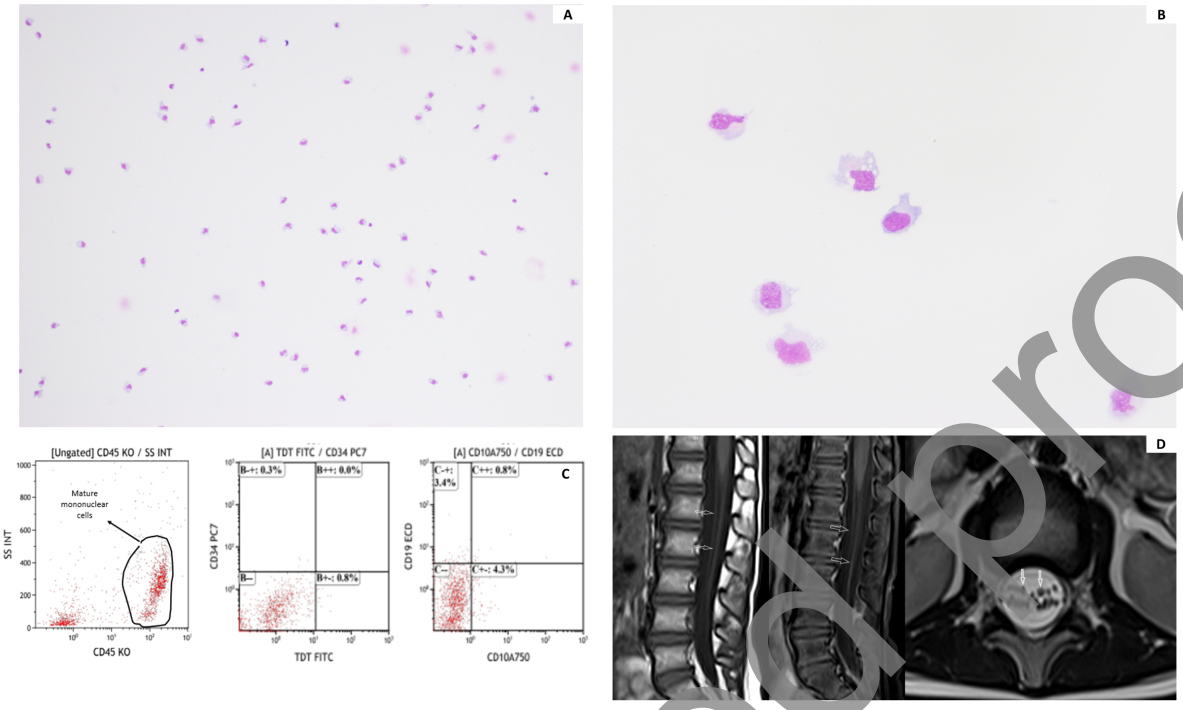
Informed consent: Informed consent was obtained from parents of patient. Parents of patients signed informed consent regarding publishing their data and photographs.

Conflicts of interest: The authors declare that they have no conflict of interest.

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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	53,00	-	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. Demonstrating abundant mononuclear cells in the cerebrospinal fluid (CSF) cytospin (Wright Stain X10) **(A)**; arachnoid cells in the CSF cytospin (Wright StainX40) **(B)**; in a flow cytometric examination **(C)**; arachnoiditis (white arrow) by magnetic resonance imaging and **(D)**; changes in CSF protein levels and the numbers of intrathecal treatment **(E)**; in a child with precursor B-cell ALL.

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