Spinal Cord Atrophy Due to Intrathecal Chemotherapy in an ALL Patient

ALL Hastasında İntratekal Kemoterapiye Bağlı Spinal Kord Atrofisi

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ABSTRACT

A 19-year-old man had been diagnosed as B-cell acute lymphoblastic leukemia and was started on chemotherapy. On the 10th day of induction chemotherapy, prophylactic intrathecal methotrexate was added to the patient's therapy regimen. After one month, left 6th and right 7th cranial nerve paralysis were developed. By suspicion of central nervous system relapses, intrathecal combined methotrexate, cytarabine and hydrocortisone had been started, and followed by cranial irradiation at 2520 cGy. Although, cranial nerve paralyses recovered without any sequela after two weeks, the patient was noted to have upper and lower extremity weakness. Cervical spinal magnetic resonance imaging demonstrated diffuse spinal cord atrophy without any leukemic infiltration. Spinal cord atrophy as a neurotoxic effect of intrathecal methotrexate and cytarabine chemotherapy should be kept in mind as an etiological factor of upper and lower extremity weakness in ALL patients.

Keywords: Spinal cord, chemotherapy, MRI

ÖZET

On dokuz yaşındaki erkek hastaya B hücreli akut lenfoblastik lösemi tanısı konarak kemoterapi başlatıldı. İndüksiyon kemoterapinin 10. gününde, hastanın tedavi rejimine profilaktik olarak intratekal metotreksat eklendi. Bir ay sonra sol 6. ve sağ 7. kranial sinirlerde paralizi gelişti. Santral sinir sistemi relapsı şüphesi ile intratekal metotreksat, sitarabin ve hidrokortizon kombinasyonu başlandı ve bunu 2520 cGy kraniyal irradiasyon izledi. Kranial sinir paralizilerinin iki hafta içinde sekelsiz olarak düzelmelerine rağmen, hastanın üst ve alt ekstremitelerinde kuvvet kaybı başladı. Servikal manyetik rezonans görüntülemede lösemik infiltrasyon olmamasına karşın yaygın spinal kord atrofisi bulguları saptandı. Üst ve alt ekstremite kuvvet kaybı olan ALL hastalarında intratekal metotreksat ve sitarabin kemoterapisinin nörotoksik etkisi olarak spinal kord atrofisi akılda tutulmalıdır.

Anahtar sözcükler: Spinal kord, kemoterapi, MRG

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To the Editor,

A 19-year-old man was admitted to our clinic complaining of weakness in upper and lower extremities. He had been diagnosed as B-cell acute lymphoblastic leukemia (ALL) type L3, 7 months ago. There were not any neurological abnormalities on physical examination at the time of his admission.

As a standard approach the patient was started on chemotherapy. On day 10th of induction chemotherapy, prophylactic intrathecal methotrexate (MTX) was added to the patient's therapy regimen. After 1 month, left 6th and right 7th cranial nerve (CN) paralysis developed. By suspicion of central nervous system (CNS) relapses, intrathecal combined MTX, cytarabine (Ara-C) and hydrocortisone had been started. The treatment regimen

was as follows: MTX 15 mg/day, Ara-C 30 mg/day, hydrocortisone 4 mg/day for two days in a week. The duration of the therapy was three weeks (total 6 doses) and intrathecal chemotherapy was followed by cranial irradiation at 2520 cGy.

Although, CN paralyses recovered without any sequela after two weeks, the patient was noted to have upper and lower extremity weakness, and eventually symptoms progressed to the point that he could not walk. His current physical examination revealed quadriparesis. Deep tendon reflexes were diminished, and Babinski's sign was indifferent symmetrically. Sensory examination showed anesthesia under the dermatome of T4. There was no urinary or bladder incontinence. Cranial magnetic resonance imaging (MRI) was unremarkable.

Cervical spinal and thoraco-lumbar spinal MRI, that performed to understand the etiology of neurological symptoms, demonstrated spinal cord atrophy without any leukemic infiltration. Cervical spinal magnetic resonance imaging (sagittal, T2 weighted) demonstrated diffuse spinal cord atrophy, particularly below the level of cervical 6th vertebra up to thoracic 3rd vertebra that could be seen on the imaging field (Figure 1). This situation was commented as the neurotoxic effect of intrathecal MTX and Ara-C chemotherapy.

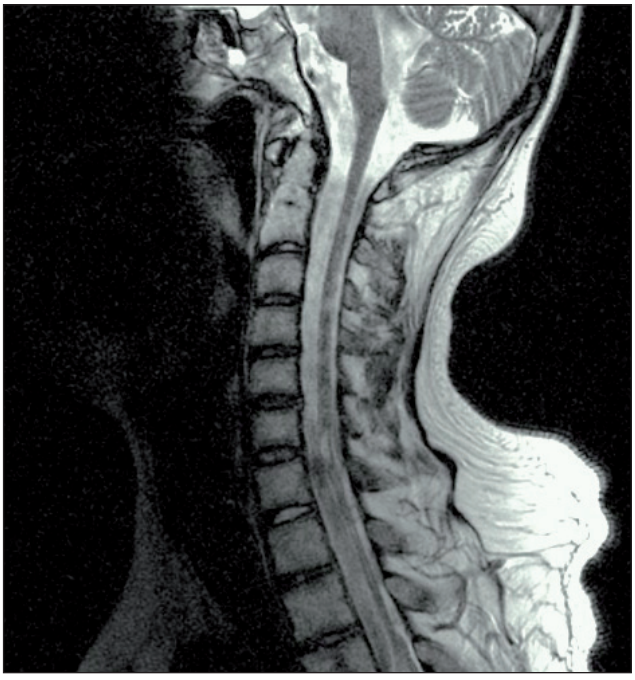

Figure 1. Cervical spinal magnetic resonance imaging (sagittal, T2 weighted) demonstrates diffuse spinal cord atrophy, particularly below the level of cervical 6th vertebra up to thoracic 3rd vertebra that could be seen on the imaging field without leukemic infiltration.

Intrathecal chemotherapy with MTX, Ara-C, or both with or without hydrocortisone is considered to be the standard of care for prophylaxis and treatment of CNS leukemia and lymphoma (1). Ara-C has a longer half-life in the CSF as compared to plasma. This property is related to the lowered activity of Ara-C deaminase in the CSF and the spinal cord, and may further explain the neurotoxicity of Ara-C. In the existing literature, patients had a history of multiple intrathecal MTX injections (5-53 times) prior to developing paraplegia. The range for a single intrathecal dose of MTX was 5-25 mg. It is suggested that the concomitant use of intravenous or intrathecal Ara-C with intrathecal MTX may enhance the neurotoxicity of MTX. The dosage range of Ara-C in concomitant use with intrathecal MTX is usually 30-170 mg, while the toxic cumulative dose of Ara-C ranges between 40 and 780 mg (2).

A nonfatal case of permanent flaccid quadriplegia after the fourth triple intrathecal chemotherapy in a 6-year-old girl with acute lymphoblastic leukemia was reported and she had no evidence of meningeal involvement. Six months after intrathecal chemotherapy, CNS magnetic resonance imaging showed severe atrophy of spine, cerebellum, and cerebral hemispheres.The writers stated that; a direct toxic effect of the intrathecal chemotherapy seemed the most likely mechanism (3).

A 53 year old Hispanic woman with acute myelogenous leukemia who developed profound weakness with cranial nerve palsies following both intravenous and intrathecal chemotherapy was presented by Rison. This was an unusual case of predominantly axonal ascending sensory motor polyradiculoneuropathy with cranial nerve involvement in an adult patient with acute myelogenous leukemia following intravenous Cytosine arabinoside and intrathecal methotrexate (4). Intrathecal chemotherapy with MTX and Ara-C could in theory cause myelopathy, although this was rarely reported in adult patients with ALL (5).

According to Clark at al. the pathogenesis of myelopathy following intrathecal chemotherapy administered by lumbar puncture included an early effect on the myelin sheath in their case (6). In an another article it is reported that; soon after completion of intrathecal injection, the patient felt numbness of his left lower limb, followed by development of paraplegia and paraesthesia of the lower parts of the body and was commented as transverse myelopathy (7). Rison stated that the polyradiculoneuropathy appears to have been secondary to predominant axonal loss rather than demyelination as reported in most other studies (4). Gosavi et al described a 42-year-old woman with acute lymphoblastic leukemia who was treated with chemotherapy consisting of intrathecal MTX who developed a progressive myelopathy. The myelopathy mimicked, radiologically,

subacute combined degeneration (SACD) of the spinal cord. According to the writers, this myelopathy mimicking subacute combined degeneration could be explained by the folate antagonism of MTX (8).

As a conclusion; intrathecal chemotherapy with MTX, Ara-C, or both with or without hydrocortisone is considered the standard of care for prophylaxis and treatment of CNS leukemia and lymphoma spinal cord atrophy (1). And as a neurotoxic effect of intrathecal MTX and Ara-C chemotherapy should be kept in mind as an etiological factor of upper and lower extremity weakness in ALL patients.

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