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CASE REPORT

A case of Cauda Equina syndrome in a leukemic patient due to intrathecal methotrexate

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ABSTRACT

The leukemias may cause neurologic dysfunction through either direct invasion of the nervous system or indirectly through cytopenias, or it may occur as a result of the necessarily vigorous treatment programs for leukemia. We report here a 24-year-old acute lymphoblastic leukemia patient who in her second cycle of hyper-CVAD chem therapy regimen (high-dose Ara-C and high-dose methotrexate) received intrathecal methotrexate and two days afterwards was diagnosed as having Cauda Equina syndrome (CES). A lumbo-sacral MRI imaging with gadolinium was performed and there was a remarkable enhancement in the Cauda Equina region, suggesting either leukemic involvement or a type of neurologic complication associated with intrathecal methotrexate treatment. To rule out leukemic involvement, a lumbar puncture was performed and the CSF was free of leukemic cells. There are cases of CES developing after spinal anesthesia reported in the literature, but this is the first report of CES due to intrathecal methotrexate.

Key Words: Cauda Equina syndrome, Intrathecal methotrexate, acute lymphoblastic leukemia, complication

ÖZET

Akut lenfoblastik lösemi hastasında intratekal metotreksata bağlı Cauda Equina sendromu

Lösemiler kendileri direk invazyon yoluyla ya da hematolojik parametrelerde oluşturdukları anomalilerle nörolojik bozukluklara yol açabildikleri gibi, lösemi tedavisinde yer alan santral sinir sistemi (SSS) profilaksi rejimleri de nörotoksisite oluşturabilmektedir. Intratekal kemoterapi, radyoterapi ve yüksek doz Ara-C ya da metotreksat içeren sistemik kemoterapiler SSS tutulumu proflaksisi veya tedavisinde etkindirler. İntratekal (IT) metotreksat tedavisi sonrası menenjial irritasyon bulgularına sık rastlanmakla beraber nadir olarak paralizi veya ensefalopati vakaları da bildirilmiştir. ALL-L1 tanısı konan 24 yaşında bir bayan hastaya Hyper-CVAD (yüksek doz Ara- C ve yüksek doz metotreksat) kemoterapi rejimi uygulanmaya başlandı. Hyper- CVAD kemoterapi rejiminin ikinci kürü sırasında, IT metotreksattan iki gün sonra hastamızda nörojenik mesane ve konstipasyon gelişti. Cauda Equina sendromu tanısı konan hastanın lumbo-sakral MRI görüntülemesinde Kauda Equina bölgesinde opaklaşma olduğu görüldü. Bu sırada yapılan lomber ponksiyon ve serebrospinal sıvı incelemesi ile bu opaklaşmanın lösemik tutuluma bağlı olmadığı kanıtlandı. Literatürde spinal anesteziye sekonder gelişen Cauda Equina sendromu bildirilmiş olsa da, vakamız intratekal metotreksat sonrası görülen ilk Cauda Equina sendromu vakasıdır.

Anahtar Sözcükler: Cauda Equina sendromu, intratekal metotreksat, akut lenfoblastik lösemi, komplikasyon

INTRODUCTION

The leukemias may cause neurologic dysfunction through direct invasion of the nervous system. The necessarily vigorous treatment programs for leukemia, including central nervous system (CNS) prophylactic regimens, can also lead to neurologic dysfunction. Leptomeningeal metastasis is primarily seen in acute lymphoblastic leukemia (ALL) [1].

Intrathecal (IT) chemotherapy, radiation therapy and systemic chemotherapy incorporating high-dose (HD) Ara-C (cytosine arabinoside) and HD methotrexate are effective modalities for both prophylaxis and treatment of CNS disease in hematologic malignancies [2]. IT methotrexate frequently causes symptoms of meningeal irritation. Occasionally, cases of weakness and paralysis, and rare instances of severe encephalopathy, may occur [3]. To our knowledge, we report here the first case of Cauda Equina syndrome (CES) due to IT methotrexate used prophylactically for CNS disease in an ALL patient.

CASE REPORT

A 24-year-old woman presented to our hospital with vaginal bleeding and malaise. Complete blood count results revealed anemia and thrombocytopenia. Her physical examination revealed hepatosplenomegaly. According to the bone marrow aspiration, biopsy and immunophenotyping results, she was diagnosed as ALL-L1 (precursor B cell ALL). Cerebrospinal fluid (CSF) was free of disease. Hyper-CVAD (cyclophosphamide-adriamycin-vincristine-dexamethasone-HD methotrexate-HD Ara-C) chemotherapy regimen was started. In the first cycle of treatment, IT CNS prophylaxis could not be given to the patient because of thrombocytopenia. In her second cycle of treatment, she was given methotrexate (12 mg) intrathecally on the second day of the regimen. CSF cytology was again negative for leukemic cells. Two days after IT methotrexate, she was unable to urinate for nine hours, so a urinary catheter was inserted and 750cc urine was emptied. At the same time, she became constipated for six days. She was diagnosed as having CES.

A lumbo-sacral magnetic resonance (MR) imaging with gadolinium was performed and there was a remarkable enhancement in the Cauda Equina region, suggesting either leukemic involvement or a type of neurologic complication associated with IT methotrexate treatment. To rule out leukemic involvement, a lumbar puncture was performed, and the CSF was free of leukemic cells.

During this period, the patient on several occasions expressed the sensation of urination, and the urinary catheter was removed, but she was repeatedly unable to urinate and the catheter was re-inserted each time. On the 21st day of treatment she was discharged from the hospital with a urinary catheter and ofloxacin 400 mg/day every other day as a prophylaxis for urinary tract infection.

On her admission for the third cycle of treatment, her urinary catheter was removed, and she was able to urinate without a problem. On the ninth day of the third cycle of hyper-CVAD chemotherapy regimen, she had dysuria. The urine culture grew *Citrobacter freundii* complex 100,000 col/ml. The micro-organism was only sensitive to piperacillin/tazobactam and amikacin. The residual urine volume was calculated to be 64.5 ml with bladder ultrasonography. After seven days of treatment with piperacillin/tazobactam and amikacin, her complaints disappeared and the control urine culture was sterile. In the following cycles, no urinary tract infection occurred, but the residual urine volume was between 40 and 60 ml in each cycle. No other IT treatment was given to her after this complication, so after the fourth cycle of treatment she was given craniospinal irradiation as CNS prophylaxis. She completed all eight cycles of treatment without urinary symptoms and at present is free of symptoms after 14 months of follow-up.

DISCUSSION

Neurologic dysfunction is a common complication of leukemia or of its treatment. It is not always possible to determine the etiology of neurologic dysfunction. Early diagnosis is essential since prompt intervention can reduce morbidity and improve quality of life [1]. Neurologic dysfunction may result from leukemic infiltration of the nervous system or as a consequence of chemotherapy or prophylactic craniospinal irradiation [1]. Our patient had neurogenic bladder and became constipated on the second day of the second cycle of hyper-CVAD chemotherapy regimen, two days after IT methotrexate administration.

According to physical examination findings, she was diagnosed as CES. The Cauda Equina

("horse's tail") is the name given to the lumbar and sacral nerve roots that continue within the dural sac caudal to the conus medullaris. The Cauda Equina nerve roots provide the sensory and motor innervation of most of the lower extremities, the pelvic floor and the sphincters. CES is a term applied to the clinical picture of perineal sensory loss with loss of voluntary control of both anal and urethral sphincter and of sexual responsiveness. Clinical signs accompanying CES may differ in each patient, but the fully developed syndrome is characterized by low-back pain, bilateral sciatica, saddle hypesthesia or anesthesia, motor weakness of lower extremities, impairment of anal, bulbocavernous, medioplantar, and Achilles tendon reflexes bilaterally, rectal and bladder sphincter dysfunction, as well as sexual impotence. CES can occur not only secondary to disc disease (severe central posterior disc protrusion) but also to other spinal canal pathologies as well. The etiologies of CES can be grouped as non-neoplastic compressive etiologies, compressive spinal tumors and non-compressive etiologies [4]. Our patient had only loss of bladder and bowel function.

Neurologic dysfunction in such a leukemic patient could be due to leptomeningeal metastasis or as a complication of IT methotrexate, because the complications occurred two days after the intervention. Leptomeningeal metastasis occurs when tumor cells enter the CSF, settle on neural structures and grow. They may involve any portion of the nervous system, including the cortical surface, spinal cord, and cranial nerves, or may even extend along nerve roots into the peripheral nerves themselves [1]. In ALL, the incidence of CNS involvement is 10% in adults. Spinal involvement with symptoms of bladder and bowel dysfunction is seen in 2% of leukemic patients with leptomeningeal metastasis. The gold standard for the detection of leptomeningeal metastasis is a positive CSF cytology [1]. CSF cytology was negative in each lumbar puncture in our patient, thus excluding leptomeningeal metastasis of ALL. IT methotrexate toxicity seemed to be the most reasonable explanation for the occurrence of this complication.

Several cases of CES developing after spinal anesthesia have been reported in the literature [5,6]. The incidence of postoperative neurological injury in patients undergoing spinal anesthesia is between 0.01 and 0.7%. Lidocaine, bupivacaine, and dibucaine are the most well-established offending agents [7]. There are many case reports pointing to the neurotoxicity of IT chemotherapy, CNS radiotherapy and systemic chemotherapy. Cases with encephalopathy, varying degrees of myelopathy and even coma and death after intensive CNS-directed therapies were reported [2, 8-11]. Koh *et al.* [12] reported three children who developed progressive paraparesis after IT methotrexate administration followed by complete or partial recovery. Gadolinium enhancement of anterior lumbosacral spinal nerve roots was demonstrated in all three patients, as in our patient. The pathogenesis of the various forms of methotrexate neurotoxicity is poorly understood. The best established cause for these symptoms is high concentrations of methotrexate in the CSF or prolonged exposure of the brain to low CSF concentrations of methotrexate. These elevated concentrations of the drug may in turn be due to impaired elimination of the drug from the CSF, which is usually due to overt CNS leukemias or to increased dosage in relation to CSF volume (due to adolescent age) [3]. Neither of these can account for the neurotoxicity in our patient. But we know that spinal cord toxicity from intensive CNS-directed therapies is multifactorial, and systemic chemotherapy, IT chemotherapy and radiation therapy are the contributing factors to the neurotoxicity [2].

Systemic HD Ara-C and HD methotrexate enter the CSF and thus can contribute to the toxicity. Methotrexate and Ara-C in CSF concentrations similar to those achieved in human therapy permeated 67-99% of the cross-sectional surface area of rabbit spinal cords within one hour. The penetration was inhomogeneous, but was highest in white matter tracts where maximum toxicity is reported in toxic myelopathies [2]. Our patient experienced the CES complication in the second cycle of the hyper-CVAD chemotherapy regimen in which HD Ara-C and methotrexate were given to the patient. These HD chemotherapeutics can be a contributing factor, but it seems unreasonable to accept them as the sole etiologic agent, since the patient received the same drugs in the same doses in the consequent fourth, sixth and eighth cycles, only without IT therapy, and no complications occurred in these cycles.

In conclusion, this is the first case of CES due to IT methotrexate treatment used prophylactically for CNS disease in an ALL patient. If a patient receiving IT methotrexate treatment develops similar symptoms, IT methotrexate can be accepted as the offending agent.

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