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Intrathecal Methotrexate-Induced Lumbosacral Polyradiculopathy: A Case Report

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Background: Polyradiculopathy caused by intrathecal methotrexate (IT MTX) is a rare and serious complication of chemotherapy. The pathophysiology involved is likely due to a drug-induced folate deficiency and subsequent local immune reaction in the spinal cord.

Case Report: The authors present a 68-year-old woman with stage I breast cancer and stage III diffuse large B-cell lymphoma who developed low back pain after IT MTX treatment. Further workup revealed diffuse rope-like thickening of the cauda equina nerve roots with subtle linear low-level leptomeningeal enhancement on magnetic resonance imaging and severe primary axonal and motor polyneuropathy affecting the upper and lower extremities on electromyography/nerve conduction studies, likely a result of IT MTX toxicity. Treatment should emphasize conservative measures. Alternatively, intravenous immunoglobulin followed by intravenous methylprednisolone can be considered.

Conclusions: Polyradiculopathy caused by IT MTX is a rare finding that can be treated. It would be beneficial to further study the effects of IT MTX and create treatment protocols for its adverse effects.

Key words: Intrathecal methotrexate, polyradiculopathy, cauda equina, cancer, case report

BACKGROUND

Intrathecal (IT) chemotherapy is commonly utilized as a prophylaxis or treatment of aggressive hematologic malignancies. A frequent complication of these cancers along with various solid tumor cancers is metastasis to the central nervous system (CNS). The purpose of IT therapy is to allow for direct penetration and maximal drug exposure into the cerebrospinal fluid (1). There are a variety of IT chemotherapies that have been formulated, but methotrexate (MTX), cytosine arabinoside, and corticosteroids are the most used drugs. With this form of drug administration comes a significantly increased chance of neurotoxicity that can manifest as, but is not limited to, cauda equina syndrome, arachnoiditis, seizures, and spinal cord toxicity (2). Given the nature of hematologic and solid tumor cancers that have metastasized, IT chemotherapy is a preferred treatment modality and has been shown to be superior to standard chemotherapy (3).

Cauda equina syndrome is defined as a dysfunction of one or more of the sacral nerve roots, S2 and below. Most commonly, it presents as severe back pain, bladder or bowel incontinence, decreased sensation of the perineum, or sexual dysfunction (4). This syndrome can either be transient if addressed in time or become irreversible (5).

Temporary or permanent paraplegia is a unique but known complication of those treated with IT MTX, with a documented incidence of < 3% (6). Many patients who experience these complications will report a sudden onset of extremity weakness and, in some cases, flaccid paralysis (7). There are also reported cases of progressive paraparesis in children receiving IT treatment for CNS leukemia (8). Multilevel radiculopathy is another rare

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complaint in those suffering from CNS toxicity. It has been suggested that the mechanism of injury could be due to an inflammatory neuropathy (9). This case report discusses a patient with a significant oncologic history who underwent IT MTX and developed complications posttreatment.

CASE PRESENTATION

The patient is a 69-year-old woman with simultaneously diagnosed stage I invasive ductal carcinoma and stage III diffuse large B-cell lymphoma who was treated with multiple rounds of chemotherapy that concluded in November 2019. Her first regimen was 2 rounds of dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and IT MTX. The patient was started on IT MTX due to the location, adjacent to a vertebral body, of the lymphoma and the high-risk features found on the biopsy. The patient's last chemotherapy was 4 rounds of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with systemic MTX, but vincristine was dropped after the first session due to neuropathy. Shortly after the conclusion of her treatments, she was hospitalized for severe deconditioning and subsequently developed low back pain. The patient presented to our clinic, in September 2022 one and a half years later, with daily, intermittent back pain that radiated into her bilateral lower extremities. Her pain was exacerbated with extension or prolonged standing and was relieved by sitting. On physical exam, the patient had 5/5 strength in the bilateral lower extremities, except for bilateral 4/5 ankle dorsiflexion worse on the right. On the American Spinal Injury Association Impairment Scale, sensation was 1/2 throughout the bilateral lower extremities, worse on the right side. Reflexes of the lower extremities were 2+ bilaterally. At that time, she was taking duloxetine 90 mg, once a day for neuropathic pain. She had no prior history of lumbar spine surgery or injections.

Given the nature of the patient's pain, we pursued further testing and imaging. Electromyography of the lower extremities revealed severe axonal sensory and motor peripheral polyneuropathy. The patient's labs were notable for an elevated erythrocyte sedimentation rate of 36 but otherwise within normal limits, including lactate dehydrogenase, white blood cell count, platelet count, and hemoglobin. Magnetic resonance imaging (MRI) of the lumbar spine without contrast revealed heterogeneous diffuse thickening of the cauda equina nerve roots with multilevel degenerative changes of the spine with varying degrees of mild-to-mild/moderate spinal canal and foraminal stenosis (Fig. 1). A repeat MRI of the lumbar spine with and without contrast showed similar cauda equina findings, but with subtle linear low-level leptomeningeal IT enhancement (Fig. 2). At that time, the differential diagnostic considerations included early leptomeningeal involvement by diffuse large B-cell lymphoma, Guillain-Barré syndrome, or a chronic inflammatory polyneuropathy (e.g., Charcot-Marie-Tooth disease or Dejerine-Sottas syndrome). However, leptomeningeal involvement by large B-cell lymphoma often produces a more striking intensity of enhancement.

Due to the patient's oncologic history, a positron emission tomography scan was done but did not reveal new cancerous lesions. In order to better characterize what was occurring in the CNS, a lumbar puncture (LP) with cytology and flow cytometry was performed, but both results were negative for acute pathology. The only significant finding of the LP was mildly elevated protein. The patient was treated symptomatically with physical therapy (PT).

The patient was last seen in our clinic in November 2022 and has been actively participating in PT since then. We have been following up peripherally with her physical therapists who report she is taking her duloxetine and regaining her strength to perform activities of daily living while reporting no pain.

DISCUSSION

IT chemotherapy is an effective form of treatment against cancer, but it comes with a multitude of side effects. Many of these side effects can be either systemic or localized to the CNS. The most common side effects of systemic MTX are gastrointestinal manifestations, fatigue, bone marrow suppression, and organ failure. Our case demonstrates a patient who developed leptomeningeal thickening of the cauda equina after being treated with multiple rounds of IT and systemic MTX. It is likely that the MRI findings were caused by IT MTX (10). There are multiple theories regarding the pathophysiology of MTX neurotoxicity, but the current leading proposals involve disruption of localized folate pathways causing: adenosine accumulation; impairment of biopterin recycling with subsequent disturbance in dopamine and serotonin synthesis; and buildup of homocysteine with unwanted byproducts of sulfur-containing excitatory amino acids (11). A 2014 study in the *Journal of Clinical Oncology* suggested that

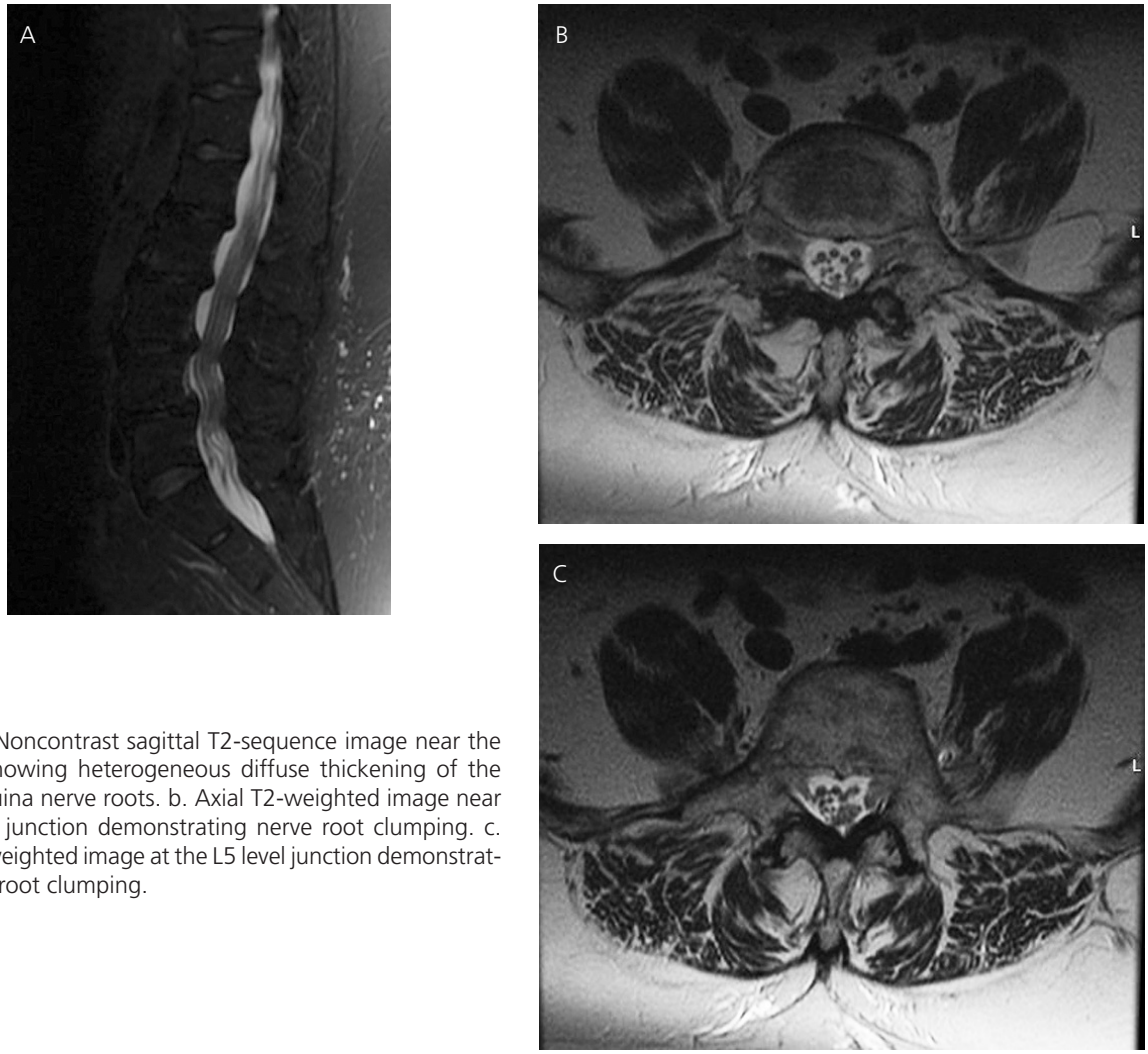

Fig. 1. a. Noncontrast sagittal T2-sequence image near the midline showing heterogeneous diffuse thickening of the cauda equina nerve roots. b. Axial T2-weighted image near the L5-S1 junction demonstrating nerve root clumping. c. Axial T2-weighted image at the L5 level junction demonstrating nerve root clumping.

genetic polymorphisms may also play a large role in neurotoxicity associated with IT MTX (12). The presence of increased protein in this patient's LP suggests that an inflammatory process may have been occurring (13).

If the patient's pain did not improve with PT and medication, our clinic would have suggested intravenous immunoglobulins followed by high-dose intravenous methylprednisolone as a previous case study (14) showed reversal of the physical manifestations of spinal cord toxicity from IT MTX with this treatment regimen. Other promising treatments for MTX neurotoxicity include supplementation of key metabolites in the methyl-transfer pathway, such as S-adenosylmethionine, folinate, cyanocobalamin, and methionine, or administering leucovorin (15,16).

CONCLUSIONS

Polyneuropathy caused by IT MTX is a rare finding but can be treated if recognized early enough. It may be beneficial to further study the complications of IT MTX and create treatment protocols for its adverse effects.

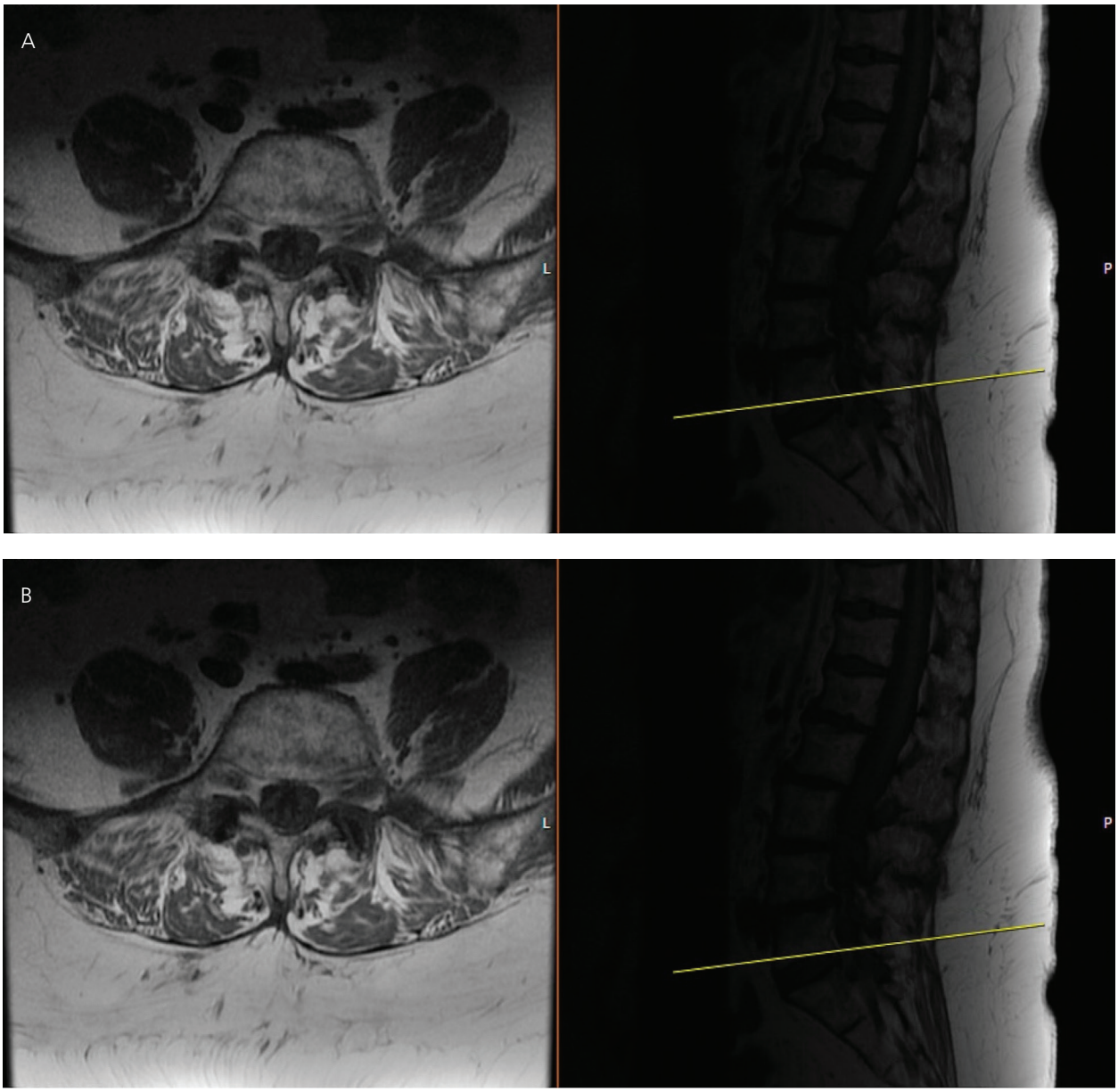

Fig. 2. A) T1-weighted images precontrast demonstrating nerve root clumping. B) T1-weighted images after intravenous contrast administration demonstrating subtle leptomeningeal enhancement.

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