Intrathecal Methotrexate-Induced Necrotizing Myelopathy: A Case Report and Review of Histologic Features

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ABSTRACT: Central nervous system (CNS) relapse of acute lymphoblastic leukemia (ALL) is associated with a poor prognosis. However, prophylactic measures, including intrathecal (IT) methotrexate, reduce the incidence of CNS relapse in these patients considerably. Unfortunately, IT methotrexate can cause several neurologic complications, including transverse myelopathy; ie, the development of isolated spinal cord dysfunction over hours or days following the IT infusion of methotrexate, but in the absence of a compressive lesion. Transverse myelopathy following IT methotrexate is a well-established clinical phenomenon, but the histologic features have been described only very rarely. We report the autopsy findings from a 31-year-old man with a history of T-cell ALL who received prophylactic IT methotrexate in anticipation of a bone marrow transplant. Microscopic examination showed transverse necrosis of the thoracic cord, with massive infiltration by macrophages and lymphocytes, and perivascular lymphocytic infiltrates. There was cavitary necrosis of cervical and lumbar spinal cord involving the entire gray matter and focal white matter, as well as extensive subpial vacuolar degeneration of the dorsal and lateral columns.

KEYWORDS: Methotrexate, intrathecal, myelopathy, vacuolar degeneration

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Introduction

Over the last 2 decades, advances in understanding the biology of acute lymphoblastic leukemia (ALL), adoption of induction and maintenance regimens based on risk-adapted strategies, improved prophylaxis, and better supportive care have generated improved survival rates in adult patients. However, the prognosis remains grim for patients who develop central nervous system (CNS) relapse, and CNS involvement continues to be a major limitation to achieving long-term cure and a primary cause of mortality.[1] Without preventive therapy, 30% to 50% of adults with ALL eventually develop CNS involvement.[2] However, following advances in chemotherapy and effective CNS prophylaxis, the incidence of CNS relapse has decreased to 5% to 10%.[2] Intrathecal (IT) chemotherapy is the preferred method for CNS prophylaxis because it bypasses the blood–brain barrier (BBB) and allows for effective treatment at a lower dose. The most widely used and effective agent is methotrexate because it persists longer in the cerebrospinal fluid (CSF) and penetrates more deeply into meninges and CNS parenchyma.[3] Unfortunately, IT methotrexate is associated with several neurologic complications, including peripheral and cranial neuropathies, acute encephalopathy, headaches, and seizures. Transverse myelopathy is a much less common but still dreaded complication of IT methotrexate and is defined as the development of isolated spinal cord dysfunction over hours or days following the IT infusion of methotrexate in the absence of a compressive lesion.[4] We report the autopsy findings of IT methotrexate-induced transverse myelopathy in a 31-year-old man with ALL.

Case Presentation

The patient was diagnosed with T-cell ALL 3 years antemortem after presenting with swollen cervical lymph nodes and a mediastinal mass. He was treated with hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone (hyper-CVAD) which resulted in a complete remission. One year antemortem he relapsed in the bone marrow and lymph nodes and was treated with additional hyper-CVAD as well as nelarabine which again resulted in remission. Five months antemortem, the patient decided to proceed with a haplo-identical bone marrow transplant. As part of the pre-transplant prophylaxis, he was given systemic hyper-CVAD as well as IT methotrexate. One day following the IT infusion of methotrexate, the patient developed motor weakness and loss of sensation in bilateral lower extremities. The IT infusion was immediately discontinued and he was infused with high dose systemic as well as IT steroids. However, his symptoms did not improve, culminating in complete paraplegia 6 days later. No blasts were seen microscopically in the CSF. Spinal magnetic resonance imaging (MRI) revealed diffuse increase in signal intensity on T2-weighted imaging extending from T1 to T11. A patchy increase in T2 signal intensity was observed within the right lateral corticospinal tract of the cervical spinal cord extending from C4 to C6. MRI of the brain was unremarkable. Based on the clinical and radiologic findings, the patient was diagnosed with transverse myelitis. He was treated with high-dose systemic and IT steroids, followed by 5 rounds of plasmapheresis and intravenous immunoglobulins (IVIG), but with no improvement. Eventually, he developed complete quadriplegia.

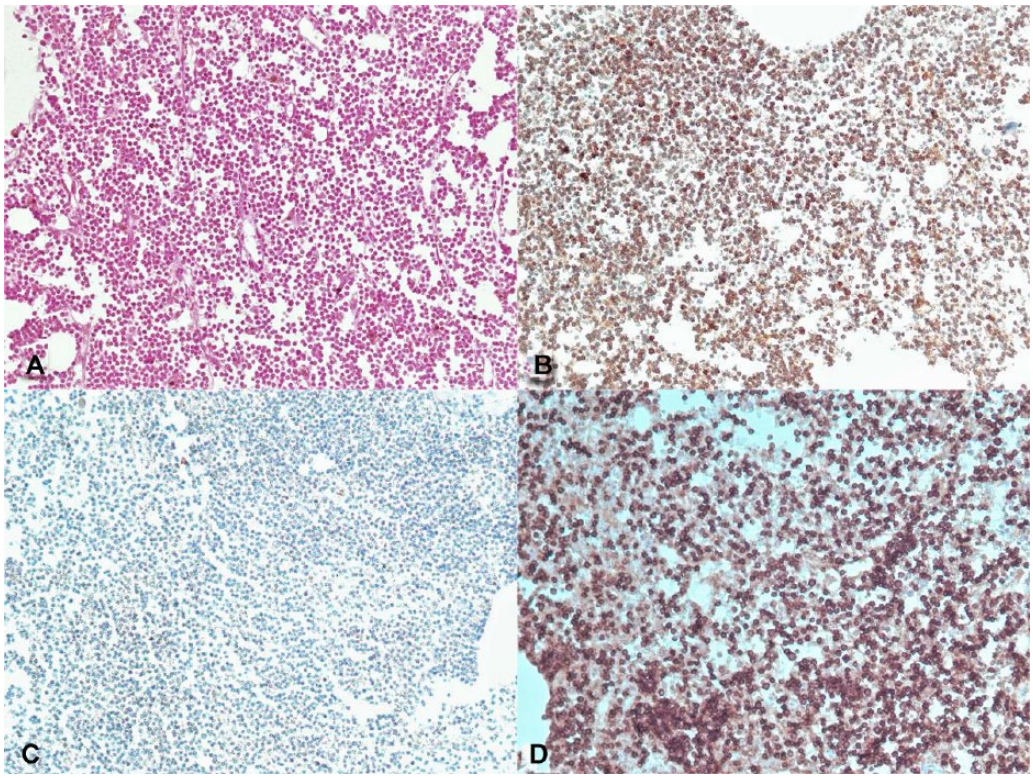

Figure 1. (A) Hematoxylin and Eosin (H&E) stained section of the vertebral bone showing a hypercellular marrow with diffuse sheets of blasts. (B) Blasts showing strong positivity for CD3 immunohistochemical stain. (C) Blasts are negative for CD20 immunohistochemical stain. (D) Blasts showing strong positivity for CD1a immunohistochemical stain.

Subsequently, the patient developed multiple decubitus ulcers leading to refractory septic shock 5 months later.

At autopsy, the external examination showed several large decubitus ulcers, including a 16 cm × 16 cm grade-IV sacral ulcer with involvement of the underlying bone. Microscopic examination showed a hypercellular vertebral marrow (>95% cellularity) mostly consisting of diffuse sheets of blasts (Figure 1A); occasional surviving myeloid and erythroid elements were also seen. The blasts were diffusely positive for CD3 (Figure 1B) and negative for CD20 immunohistochemical stain (IHC) (Figure 1C). CD1a was expressed in more than 80% of the cells (Figure 1D) while CD8, CD34, and terminal deoxynucleotidyl transferase (TdT) IHCs were negative. Extensive leukemic infiltration was also seen in bilateral kidneys, spleen, and lymph nodes.

The spinal cord was removed. Grossly, the dura surrounding the cord was thickened and focally calcified, with extensive adhesions to the surrounding bone and soft tissue structures. The thoracic spinal cord showed marked softening. No mass lesions or areas of compression were seen at any level. The vertebral column was intact throughout without evidence of degenerative changes. Representative microscopic sections of the spinal cord showed transverse necrosis of the thoracic cord and patchy necrosis and vacuolar degeneration involving the gray as well as the white matter of the cervical and lumbar cord. No leukemic infiltrates were seen in the gray matter, white matter, or the leptomeninges.

Histologic features of drug toxicity were restricted to the spinal cord. The brain weighed 1420 g and showed no gross abnormalities. Representative sections of the medulla, pons, midbrain, basal ganglia, cerebral cortex, hippocampus, and cerebellum showed no evidence of toxicity or involvement by leukemia.

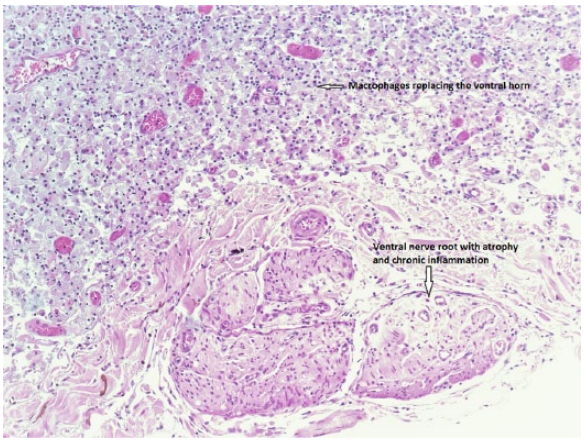

Figure 2. Section of thoracic spinal cord showing replacement of ventral horn cells by sheets of macrophages and end-stage atrophy of the corresponding ventral nerve root

The thoracic spinal cord showed the most extensive damage, with sheets of foamy macrophages and scattered lymphocytes forming large cavitary spaces replacing almost the entire gray and the white matter space. No surviving ventral horn cells were seen in the thoracic cord, and the corresponding ventral nerve roots showed end-stage atrophy with focal lymphocytic inflammation (Figure 2). The resorbing macrophages and lymphocytes also replaced the entire gray matter as well as the

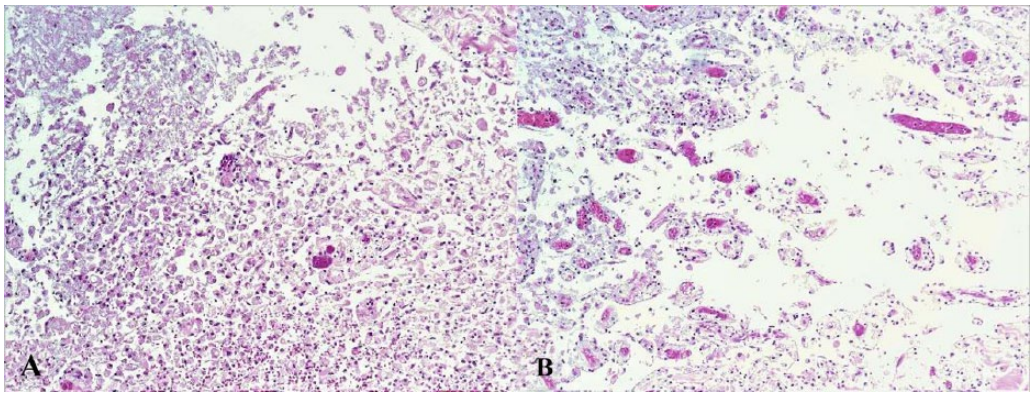

Figure 3. (A) Section of thoracic spinal cord showing complete replacement of gray matter by macrophages and lymphocytes. (B) Section of thoracic spinal cord showing complete loss of white matter in the dorsal column.

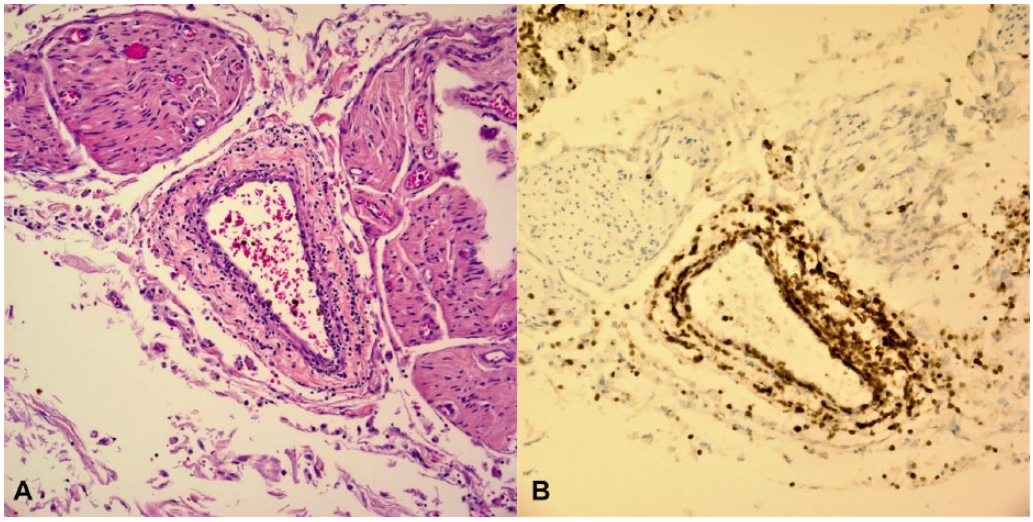

Figure 4. (A) A blood vessel showing prominent perivascular lymphocytic infiltrate. (B) The perivascular lymphocytes are positive for CD3 immunohistochemical stain.

lateral and dorsal columns of the white matter (Figure 3A and B). Most blood vessels in the spinal cord showed prominent perivascular lymphocytic infiltrates of CD3-positive T-lymphocytes (Figure 4). Fibrinoid necrosis, vessel wall inflammation, and calcification were not seen. CD68 IHC showed a diffuse sheet of macrophages involving approximately 80% of the cord space (Figure 5). The lymphocytes stained positive for CD3 and negative for CD1a, differentiating them from leukemic blasts. Neurofilament protein and glial fibrillary acidic protein (GFAP) IHCs showed near complete loss of axons and astrocytes throughout the thoracic cord.

The cervical spinal cord showed extensive necrosis of the gray matter extending into the surrounding white matter (Figure 6). The white matter of the cervical cord showed focal necrotic areas of varying sizes consisting of resorbing macrophages, lymphocytes, and neuronal debris in the lateral and dorsal columns (Figure 7). The surviving white matter showed patchy areas of vacuolar degeneration which were particularly centered in the subpial region. Luxol fast blue (LFB) stain showed loss of myelin in these degenerated areas (Figure 8). The lumbar spinal cord showed complete obliteration of the gray matter by a large cavitary space consisting of macrophages and neuronal debris. The white matter showed relative preservation with focal areas of necrosis and vacuolar degeneration similar to the cervical cord. Occasional surviving anterior horn cells were seen in the anterior horn with the corresponding ventral nerve roots showing moderate atrophy.

Discussion

The CNS serves as a sanctuary site for leukemic cells due to the limited penetration of intravenous anti-neoplastic drugs across the BBB into the CSF and brain parenchyma. The insufficient CNS accumulation of the drugs conventionally used to treat ALL explains why, in the absence of adequate IT prophylaxis, recurrence at this site is observed in approximately 30% to 50% of adult patients.[2,5] Effective CNS prophylaxis has decreased the incidence of CNS relapse in cases of ALL to 5% to 10%.[6] Unfortunately, systemic and/or IT methotrexate administration is associated with severe neurotoxicity, which can be divided into acute, subacute, and chronic forms based on the time of appearance of symptoms after administration. Acute toxicity manifests during or within hours following methotrexate infusions and is characterized by somnolence, confusion, headache, nausea, and dizziness. Subacute neurotoxicity is usually observed

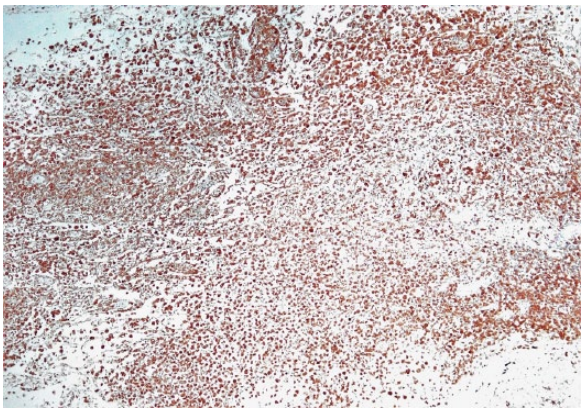

Figure 5. CD68 immunohistochemical stain showing numerous macrophages in the thoracic spinal cord.

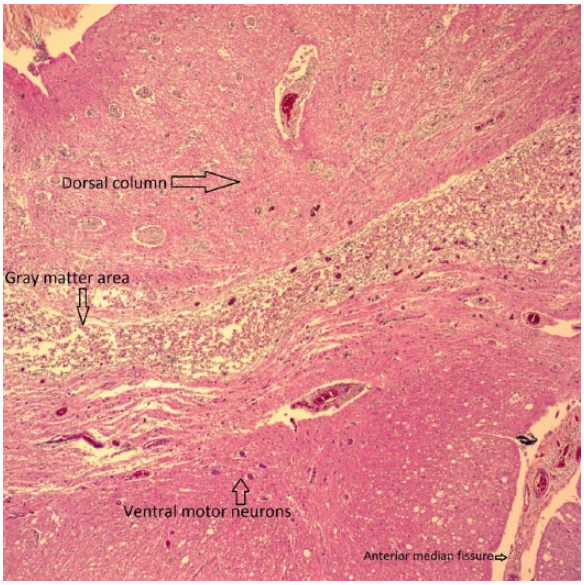

Figure 6. Section of cervical spinal cord showing extensive necrosis of the gray matter extending into the surrounding white matter.

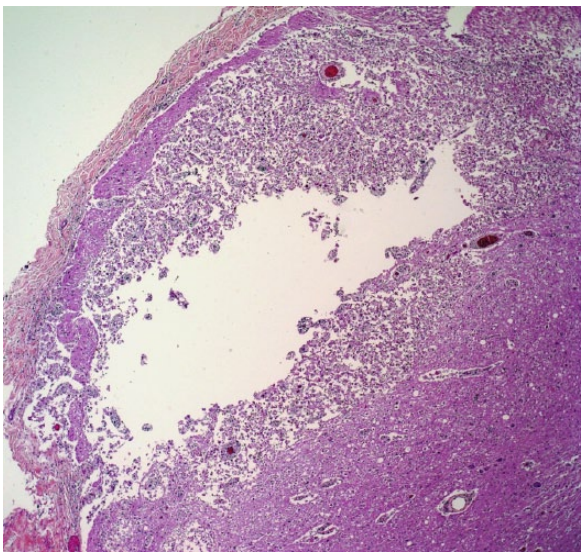

Figure 7. Section of cervical spinal cord showing an area of cystic necrosis consisting of resorbing macrophages, lymphocytes, and neuronal debris in the lateral column.

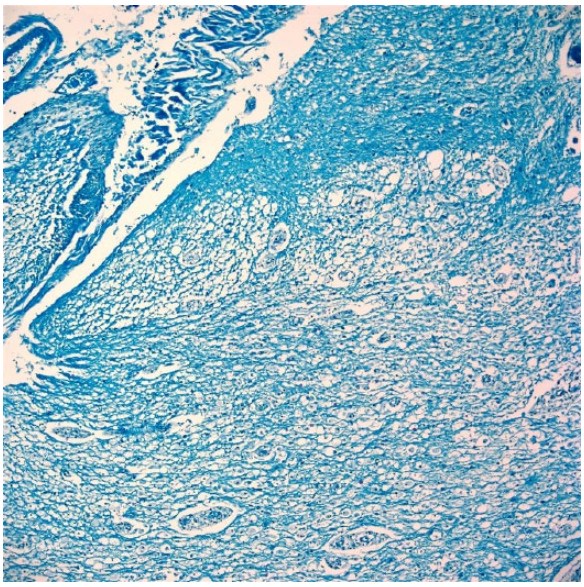

Figure 8. Luxol Fast Blue (LFB) stain showing subpial vacuolar degeneration and loss of myelin in the dorsal column of cervical spinal cord.

days to weeks following methotrexate infusion and manifests as seizures, hemiparesis, speech disturbances, and myelopathy, especially following IT infusion. Chronic neurotoxicity may occur after months to years and is usually associated with leukoencephalopathy, which can be transient and nonsymptomatic or severe, characterized by personality changes, progressive dementia, focal seizures, spastic quadriparesis, and stupor.[6]

Transverse myelopathy is a rare subacute complication of IT methotrexate, with a reported incidence of 3%.[4] It is defined as the development of isolated spinal cord dysfunction over hours or days following the IT infusion of methotrexate in the absence of a compressive lesion. Our patient exhibited typical clinical and radiologic features of transverse myelopathy 1 day following IT infusion. Multiple case reports of transverse myelopathy following IT methotrexate have appeared in the literature,[7–11] but the histologic features of this phenomenon have been described only rarely and are not well established. In most reported cases, the symptoms were reversible, but in some, the neurologic symptoms progressed over hours or days, resulting in permanent deficits as in this case.

The pathogenesis of methotrexate-induced myelopathy is not fully understood, but there are indications that drug-induced biochemical alterations play an important role. Methotrexate is a folic acid antagonist that inhibits DNA synthesis through inhibition of enzyme dihydrofolate reductase. Disturbance of folic acid metabolism induced by methotrexate also indirectly inhibits the synthesis of methionine. The lack of methionine disturbs the methyl-transfer pathway, leading to reduced synthesis of the S-adenosylmethionine (SAM) which is necessary for the formation and maintenance of myelin sheaths. This loss of myelin most likely leads to the vacuolar degeneration of the white matter.[12,13] It has been shown recently that administration of high doses of the key metabolites of the methyl-transfer pathway (SAM, folinate, methionine, and cyanocobalamin) following the

appearance of symptoms can reverse the toxicity, resulting in marked clinical improvement.[14]

Another mechanism that possibly plays a role in methotrexate-induced myelopathy is the direct toxic effect of methotrexate on the endothelial cells of the venules and capillaries. The vascular injury allows the drug to diffuse deeply into CNS parenchyma and directly exert its toxic effects, which manifest as necrosis and vacuolar degeneration.[15,16] Vascular abnormalities associated with methotrexate toxicity, such as fibrinoid necrosis, non-inflammatory mineralizing angiopathy, and thrombosis, have been described in the literature[17] but are seen in the acute phase of drug toxicity. This case showed prominent perivascular lymphocytic infiltrates but no necrosis or inflammation of the vascular wall, possibly because the autopsy was performed 5 months post insult.

The major pathologic findings that have been described for IT methotrexate-induced myelopathy are transverse necrosis, particularly involving the thoracic cord, infiltration by lipid-laden macrophages, and vacuolar degeneration of the subpial white matter in association with severe loss of axons and myelin sheaths.[8,10,18] This case also showed transverse necrosis of the thoracic spinal cord and vacuolar degeneration with loss of myelin in the white matter of the cervical and lumbar cord. In addition, the cervical and lumbar cords showed areas of patchy cavitary necrosis as well. Lipid-laden macrophages were plentiful in the necrotic areas. Previous cases have described a relative preservation of the gray matter[19]; however, in our case, loss of the gray matter was observed throughout the spinal cord. Reactive astrocytosis, dystrophic calcification, and vascular abnormalities including fibrinoid necrosis, non-inflammatory mineralizing angiopathy, and thrombosis have been described in the literature but were not seen in this case.

Summary

We describe the histologic features of IT methotrexate-induced myelopathy in a 31-year-old man with ALL. Myelopathy is a rare but grave complication of IT methotrexate infusion. The symptoms typically appear days to weeks following infusion and are reversible with drug cessation in most cases. However, some cases show progression of symptoms leading to an irreversible loss of neurologic function, as in this case. The main pathologic findings seen in this case were transverse necrosis of the thoracic cord with massive infiltration by macrophages and reactive lymphocytes and perivascular lymphocytic infiltrates. There was cavitary necrosis of cervical and lumbar spinal cords involving the gray matter entirely and white matter focally as well as extensive subpial vacuolar degeneration. Although the incidence of methotrexate-induced transverse myelopathy is low and the mechanisms behind it are poorly understood, physicians must be aware of this complication because it is potentially reversible with early recognition, cessation of chemotherapy, and prompt administration of high-dose steroids and/or high doses of the key metabolites of the methyl-transfer pathway.

Author Contributions

FS performed the autopsy and was assisted by HT. HT did the literature search and wrote the manuscript. AG was the consulting neuropathologist on the case. FS and AG edited the manuscript.

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REFERENCES

1. Del Principe MI, Maurillo L, Buccisano F, et al. Central nervous system involvement in adult acute lymphoblastic leukemia: diagnostic tools, prophylaxis, and therapy. *Mediterranean J Hematol Infect Dis*. 2014;6:e2014075.
2. Pan Y, Wang C, Wang H, Tao Q_, Xiong S, Zhai Z. Transverse myelopathy occurring with intrathecal administration of methotrexate and cytarabine chemotherapy: a case report. *Oncol Lett*. 2016;11:4066–4068.
3. Blasberg RG, Patlak C Fenstermacher JD. Intrathecal chemotherapy: brain tissue profiles after ventriculocisternal perfusion. *J Pharmacol Exp Ther*. 1975;195:73–83.
4. Teh HS, Fadilah SAW, Leong CF. Transverse myelopathy following intrathecal administration of chemotherapy. *Singapore Med J*. 2007;48:e46–e49.
5. Gökbuget N, Hoelzer D. Meningeosis leukaemica in adult acute lymphoblastic leukaemia. *J Neurooncol*. 1998;38:167–180.
6. Vezmar S, Schusseler P, Becker A, Bode U, Jaehde U. Methotrexate-associated alterations of the folate and methyl-transfer pathway in the CSF of ALL patients with and without symptoms of neurotoxicity. *Pediatr Blood Cancer*. 2009;52:26–32.
7. Yim YS, Mahoney DH Jr, Oshman DG. Hemiparesis and ischemic changes of the white matter after intrathecal therapy for children with acute lymphocytic leukemia. *Cancer*. 1991;67:2058–2061.
8. Clark AW, Cohen SR, Nissenblatt MJ, Wilson SK. Paraplegia following intrathecal chemotherapy. Neuropathologic findings and elevation of myelin basic protein. *Cancer*. 1982;50:42–47.
9. von der Weid NX, de Crousaz H, Beck D, Deonna T, Miklossy J, Janzer RC. Acute fatal myeloencephalopathy after combined intrathecal chemotherapy in a child with acute lymphoblastic leukemia. *Med Pediatr Oncol*. 1991;19:192–198.
10. Honda D, Ochiai J, Ujihira N, Yoshida M, Sobue G. Methotrexate myelopathy. *Neurol Med (Tokyo)*. 2012;77:35–42.
11. Grisold W, Lutz D, Wolf D. Necrotizing myelopathy associated with acute lymphoblastic leukemia. *Acta Neuropathol*. 1980;49:231–235.
12. Linnebank M, Pels H, Kleczar N, et al. MTX-induced white matter changes are associated with polymorphisms of methionine metabolism. *Neurology*. 2005;64:912–913.
13. Barber JR, Clarke S. Inhibition of protein carboxyl methylation by S-adenosyl-L-homocysteine in intact erythrocytes. *J Biol Chem*. 1984;259:7115–7122.
14. Ackermann R, Semmler A, Maurer G. Methotrexate-induced myelopathy responsive to substitution of multiple folate metabolites: a case report. *J Neuro-Oncol*. 2010;97:425–427.
15. Shibutani M, Okeda R. Experimental study on subacute neurotoxicity of methotrexate in cats. *Acta Neuropathol*. 1989;78:291–300.
16. Suzuki K, Takemura T, Okeda R, Hatakeyama S. Vascular changes of methotrexate-related disseminated necrotizing leukoencephalopathy. *Acta Neuropathol*. 1984;65:145–149.
17. Ellison D, Love S, Cardao LM, et al. *A Reference Text of CNS Pathology*. 3rd ed.; Mosby Elsevier, 2012.
18. Tomonaga M, Takeno Y, Ishii N, Okayama M. Paraplegia following intrathecal methotrexate. *Adv Neurol Sci (Tokyo)*. 1978;22:1204–1211.