Case Report

Progressive motor polyradiculopathy and myelopathy associated with lymphoma and intrathecal methotrexate treatment, a case report and systemic review

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Abstract:
We report a patient with Burkitt's lymphoma involving the liver and retroperitoneal lymph nodes who developed acute, progressive, quadriplegia associated with sphincter dysfunctions and an ascending sensory level after the 2nd dose of intrathecal methotrexate. The motor deficits and the spinal dysfunction persisted in spite of discontinuation of the methotrexate, as well as treatments with intrathecal steroids, pulse intravenous steroids, and intravenous immunoglobulin. The status of the lymphoma was improving on systemic chemotherapy. Whether the progressive motor neuropathy and progressive myelopathy are a toxicity of intrathecal methotrexate or a paraneoplastic phenomenon is a matter of debate.
Key words: Lymphoma, intrathecal chemotherapy, methotrexate, toxicity, paraneoplastic.

Introduction:

Neurological complications of lymphoma are not rare. Usually they are secondary to involvement of the brain with the disease, or infiltration of the meninges or nerve roots with lymphomatous cells. Peripheral nervous system pathology can occur as a direct effect of the systemic or intrathecal chemotherapy. Nevertheless, there are several reports of disease of the central and peripheral nervous systems in association with lymphoma either as a paraneoplastic syndrome or idiosyncratic effect of the intrathecal treatment (1). We present a case of progressive myelopathy and motor polyneuropathy associated with lymphoma and following intrathecal chemotherapy who deteriorated in spite of tumor regression and interruption of treatment.

Case Report:

We report the case of a 45 year old man, known case of p-ANCA vasculitis with secondary end stage renal failure who underwent renal transplantation and was maintained on immunosuppressants.

June 2009 the patient complained of abdominal pain. CT abdomen revealed multiple liver lesions and retroperitoneal lymphadenopathies. Liver biopsy diagnosed Burkitt's lymphoma. Bone marrow biopsy

Table 1: Description of symptoms and signs, pathology and pathological findings in patients who developed neurological disorders after intrathecal Methotrexate treatment for malignancies. according to several authors.

Pathology	Neuropathological findings	Symptoms and signs	References
Myelopathy	Myelin necrosis. Microvacuolization in spinal cord	Lower extremity weakness Sensory level Sphincter dysfunction	McLean et al. 1994 (2) Geiser et al. 1975 (3) Clark et al. 1982 (5)
Myelopathy	Demyelination of white matter Scattered axonal swelling in spinal cord and brainstem	Brainstem dysfunction Quadriplegia Respiratory failure	Werner et al 1988 (4)
Motor neuron disease	Atrophy of anterior horn cells Axonal degeneration Vacuolization of spinal cord	Generalized weakness Preserved sensory exam Absent deep tendon reflexes	Pascual et al 2008 (9)
Myelopathy and polyneuropathy	Myelin degeneration Axonal degeneration Dense lipid rich macrophages and lymphocytic infiltration in peripheral nerves.	Weakness, sensory deficits, areflexia, myotonia, ataxia, unsteady gait	Toothaker et al. 2009 (12) Peress et al. 1979 (14)

and aspirate were negative for malignancy. Baseline CSF studies revealed no white blood cells or malignant cells with normal protein and sugar. The patient was treated with Rituximab and hyper CVAD regimen, along with the standard prophylaxis for central nervous system lymphoma including preservative-free intrathecal methotrexate and cytarabine injections.

Four days after the second injection of 12 mg intrathecal methotrexate the patient started developing pain and paresthesias in the feet and hands which progressed quickly and ascended to the upper thighs and forearms. At the same time he developed urinary and stool retention and incontinence. Neurological examination revealed marked decrease in tone and power in the muscles of the legs and feet more pronounced distally, areflexia in the lower extremities And absent anal tone and a T-10 sensory level.

MRI spine and CSF studies were normal. EMG of the lower extremities revealed acute demyelination of the LV and S1 motor roots bilaterally with no evidence for axonal degeneration and intact sensory fibers. CT abdomen showed regression in the size and number of the liver lesions. The patient received his scheduled systemic chemotherapy as well as another dose of intrathecal methotrexate, and intravenous pulse steroid therapy, suspecting the lumbosacral root pathology to be secondary to infiltrative disease. The patient's kidney function was normal and he did not require dialysis.

Three weeks later the patient presented with flaccid paraplegia with ascending sensory level up to T-5 level and weakness and sensory deficits in the forearms and hands bilaterally.

MRI of the spine revealed diffuse T2 high signal in the white matter distribution of the spinal cord mainly along the posterior column extending from T6 to the cauda equina with no enhancement after contrast administration. EMG revealed progression of the demyelinating motor polyneuropathy in the four extremities as well as dysfunction in the central sensory and motor tracts diagnosed by abnormal posterior tibial sensory evoked potentials and abnormal motor evoked potentials. CSF studies revealed 6 WBC all polymorphoneutrophils, elevated protein at 0.74 mg/dl and elevated IgG index at 0.92 %, oligoclonal bands were negative and still no malignant cells were seen. Chemistry and serology screening for vasculitidies were normal. No systemic of CSF evidence for an underlying infectious process could be confirmed.

Three weeks later the patient developed atrophy and weakness up to the shoulder girdle muscles and a rise in the sensory level up to T3. MRI revealed expansion

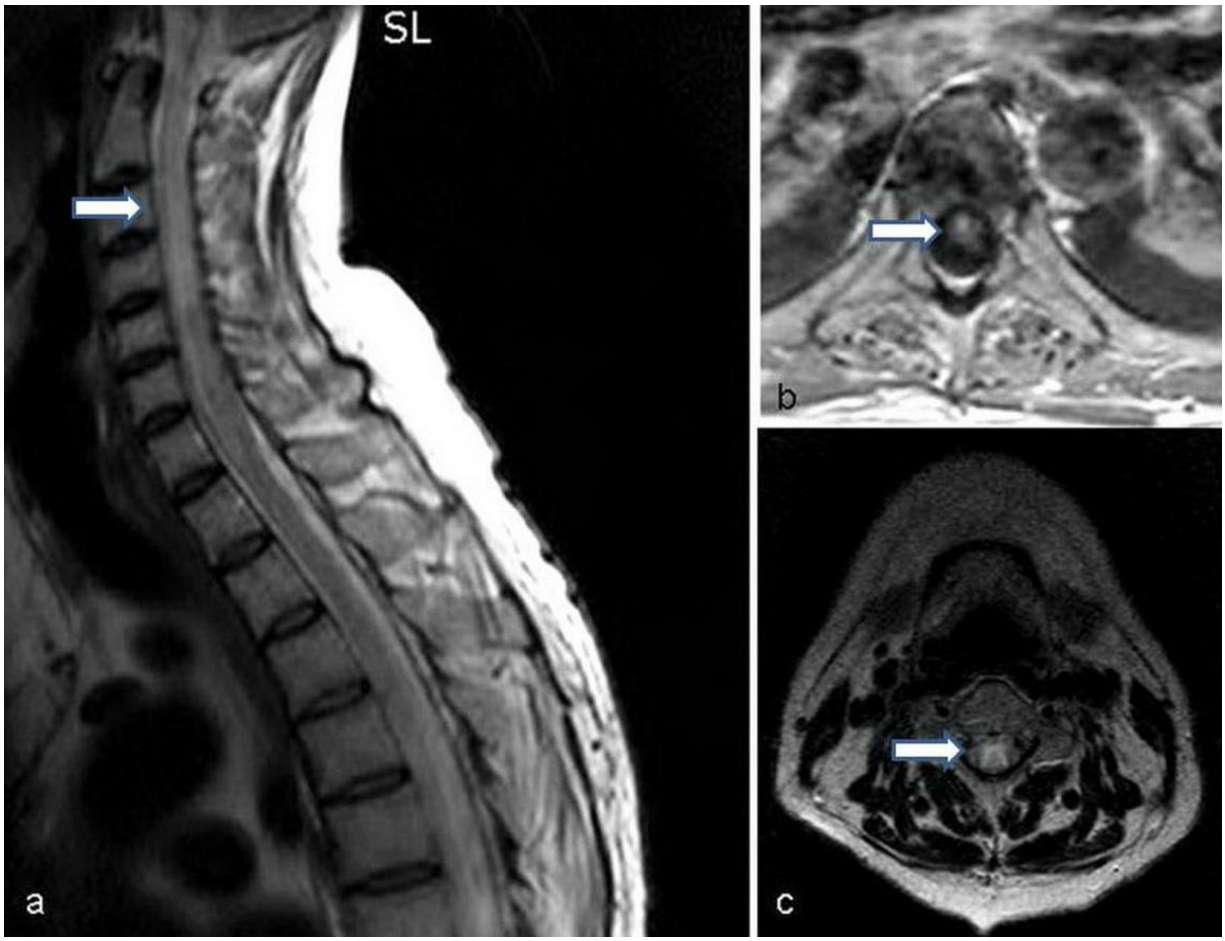

Figure 1: Abnormal swelling of the cervical cord and abnormal enhancement of the grey matter in the dorsal cord.
a. Sagittal T2 weighted image (WI) of the cervical and upper dorsal spine reveals (arrow) swelling and abnormal high signal of the cervical cord.
b. Axial enhanced T1 WI at the level of the thoracic spine demonstrates enhancement along the anterior aspect of the cord (arrow)
c. Axial T2 WI of the cervical spine shows high signal intensity involving the grey matter (arrow).

of the cord with diffuse T2 high signal intensity involving the grey matter most prominent in the cervical region. There was a small focus of bleed within the cord at T12 level and diffuse enhancement after contrast administration along the anterior aspect of the thoracic cord. (Fig 1). CSF showed 256 WBC all polymorphoneutrophils, 256 RBC, protein 0.96 mg/dl, glucose 37/110, no malignant cells, and negative gram stain and culture. The elevated polymorphoneutrophils with negative cultures could be an inflammatory response to the myelopathy and radiculopathy irrespective of the etiology. The patient received a 5 days course of IVIG 0.4 gms/kg/day as well as intrathecal 2 mg dexamethasone. Serum CMV, antiHu, antiYo and antiCRMP5 antibodies, as well as CSF AntiHu were all negative.

The patient eventually died few weeks later secondary to respiratory failure and cardia arrest. No autopsy was performed.

Discussion:

The interesting findings in the case we are presenting is the fact that the patient developed subacute, progressive, myelopathy and demyelinating motor polyneuropathy at the same time.

The difficulty is in the diagnosis of whether this severe progressive central and peripheral nervous system dysfunction is secondary to intrathecal methotrexate toxicity or a paraneoplastic phenomenon.

Intrathecal methotrexate is a treatment which has been reported to produce myelopathy and rarely radiculopathy. The myelopathy occurs in less than 3 % of patients treated with intrathecal methotrexate (2,3). It is usually self limiting or reversible in most cases. The myelopathy can occur after a single or multiple intrathecal injections (4). The pathological mechanism is unclear and occurs with or without the use of preservatives in the injected fluid. Some authors claim local depletion of folate secondary to methotrexate as a contributing factor in the myelopathy (5,6,7,8) (table 1).

Intrathecal methotrexate may cause a break down of the blood-brain barrier of the nerve roots of the cauda equine in the region where methotrexate is injected. The disruption of the blood-nerve barrier may facilitate the direct toxic effect of methotrexate at the local region or may also provoke an immune response (9). The pathological effect of intrathecal methotrexate can be attribute also to folate deficiency, the presence of neurotoxic preservatives in commercially available preparations, or the use of diluents with non-physiologic ph, abnormal iron content or altered osmolarity (10,11) (table 1).

Degeneration of central and peripheral nervous system has also been considered as a paraneoplastic phenomena in patients with lymphoma. Paraneoplastic neurologic syndromes are symptoms and signs of a neurologic disorder that occur in association with an underlying malignancy without being directly caused by the malignancy itself as in infiltration or compression. They are usually associated by the presence of onconeural antibodies (anti-Hu, antiYo, anti CV2, anti Ro, antiMa2, antiamphyphysin) (12,13).

Paraneoplastic myelopathy is observed with CSF findings are usually normal or with mildly elevated protein content and mild pleocytosis. No malignant cells are present in the CSF and no oligoclonal bands. No evidence for tumor cells or a vasculitic process in the affected tissues.

In our case the patient developed symptoms of myelopathy and motor polyneuropathy few days after the intrathecal injection of his second dose of methotrexate. The symptoms kept progressing until the patient became quadriplegic with a sensory level at the upper thoracic cord in-spite of discontinuation of intrathecal chemotherapy, as well as systemic and intrathecal high-dose steroid treatment, and a course of intravenous immunoglobulin. MRI of the spine revealed evidence of involvement of grey matter and posterior cord white matter. EMG studies revealed involvement of the myelin of the motor roots, sparring the motor axons and all the sensory fibers. Posterior column and lateral cord functions were disturbed as evidenced by sensory and motor evoked studies. CSF studies repeatedly revealed normal WBC count, slightly elevated protein level and no malignant cells. All studied onconeural antibodies were absent and the patient worsened in spite of improvement of his lymphoma.

Considering the above the pathology of the nervous system can not be exclusively attributed neither to a paramalignant phenomenon nor to be secondary to the toxicity of methotrexate which has been discontinued early in the course of the illness. The patient's symptoms progressed in spite of high dose steroid treatment which is described to be the therapy for such toxicity. Furthermore, no cancer cells where detected in the CSF to consider this to be directly the effect of the lymphoma invading the nervous system and the patient progressed in-spite of the regression of his cancer.

Perez et al 1979 (14) reported 2 cases of progressive myelopathy and radiculopathy in patients with untreated lymphoma. Thus, progressive myelopathy and demyelinating radiculopathy are diseases that are associated with lymphoma and its treatment either as a direct effect of the treatment or a paraneoplastic association with the cancer.

Abbreviations:

ANCA: anti nuclear cytoplasmic antigen
CMV: cytomegalovirsus
CSF: cerebrospinal fluid
CT: computerized tomography
CVAD: cyclophosphamide vincristine,adriamycin dexamethasone
EMG: electromyography
IVIG: intravenous immunoglobulin
MRI: magnetic resonance imaging
RBC: red blood cells
WBC: white blood cells

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