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Intrathecal Methotrexate Causing Paraplegia in a Middle-Aged Woman

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To the Editor

The treatment and prophylactic therapy of meningeal leukemia with intrathecal (IT) methotrexate (MTX) in acute lymphoblastic leukemia is a well-established procedure. However, attention must be paid to the increasing number of reports of serious complications due to IT MTX (1). The present work describes a 46-year-old woman suffering from acute lymphoblastic leukemia, who slowly developed progressive permanent flaccid paraplegia post MTX treatment and a rise in CSF protein level during that therapy.

Case Report

A 46-year-old woman with acute lymphoblastic leukemia received treatment with prednison, 6 MP, cytosin-araboside and later vincristine. Complete hematological and clinical remission was achieved.

Half a year later, the patient complained of severe headache, but neurological examination revealed no pathology. A lumbar puncture showed the presence of lymphoblasts in CSF. Five IT injections of 20 mg MTX with parabens preservative in 20 ml of normal saline were administered over a 2-week period. The lymphoblasts in CSF disappeared and the protein level rose from 80, 65, 135, to 400 mg/dl while the white blood cells changed from 58, 12, 113 to 60/wl. The patient received cranial irradiation of 2,400 rad.

1 day after the last IT MTX injection the patient began complaining of weakness and pains in both legs. Over a 3-week period she developed flaccid paraplegia with a sensory level at D10, accompanied by stool and urinary incontinence, and finally right arm weakness. Partial remission of the neurological disturbances was observed in the next 6 months.

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The patient died from septicemia, after the reappearance of the leukemia. Permission for autopsy was denied.

Discussion

Paraplegia complicating IT MTX treatment has been reported mainly in children and teenagers and in a few adults [1]. The toxic neurological reaction to MTX therapy can be classified into three groups according to the clinical manifestations [2]: Chemical arachnoiditis, encephalopathy and myelopathy. In myelopathy direct damage to the spinal cord or root nerves may cause serious consequences; such as paralysis, transient or permanent paraplegia, quadriplegia and even death. This complication may perhaps be partially preventable.

Different predisposing factors were suggested to be responsible for the development of these neurological complications [1]. These include the chemical preservatives, diluents, and contaminants of MTX. Comparison of 5 patients with severe neurotoxic manifestations post-IT MTX with 20 asymptomatic patients receiving the same therapy, showed that the toxic patients

were significantly older and had overt meningeal leukemia [3]. The same characteristics were found in our patient. Furthermore, neurotoxic symptoms occurred in the presence of elevated CSF concentrations of MTX. Therefore, it is suggested that frequent monitoring of CSF MTX concentration may be predictive of serious neurotoxicity and drug dosage and drug interval be adjusted accordingly [3]. However, neither the minimal effective concentration of MTX in CSF nor the toxic concentration is known [4] and therefore can not yet serve as a safe guide in treatment or prevention of the neurological complications.

In a recent review of the literature Gagliano and Costanzi [1] found 10 cases of paraplegia following IT MTX therapy and added 1. CSF examinations during IT MTX therapy have been reported in detail in only 2 patients [5].

The elevation of proteins in Luddy's case [5] before the onset of paralysis was 33, 75, 500 mg/dl and in our case 80, 60, 135 mg/dl. Generally, abnormal spinal fluid findings (proteins, cells) respond to IT MTX therapy by decreasing or disappearing. There was no other explanation for the rise of proteins in our case except MTX neurotoxicity, as there was no evidence of infection (including TBC), hemorrhage, subarachnoid block (normal myelography) or even arachnoiditis. While there is no one specific reliable indicator of a possible neurotoxic reaction, the discrepancy be-

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tween proteins and cells may perhaps serve to warn the physician of impending trouble.

It is suggested that a worsening of the neurological condition, or an increase in CSF protein (protein cells dissociation) or pressure during IT MTX therapy be taken as an indication to delay further injection, in order to diminish or avoid severe neurological complications.

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