A woman who couldn’t speak: report of methotrexate neurotoxicity

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The association between methotrexate therapy and idiosyncratic neurological complications is well recognised in children. This case illustrates the importance of considering the diagnosis of methotrexate toxicity in an adult patient with behavioural and speech disturbances, who received it by intrathecal route only and in whom the only indicator was an abnormal electroencephalographic study.

The differential diagnosis of neurological abnormalities in patients with haematological malignancy undergoing chemotherapy is very broad. Vascular, infectious, metabolic, malignant, and drug related causes need to be considered and investigated. Often diagnosis is achieved by gradual elimination of various possibilities. In this case report we present a patient whose neurological illness was felt to represent methotrexate neurotoxicity. The nature and possible causes of neurotoxicity of this drug are discussed and the diagnostic difficulties are illustrated.

CASE REPORT

A 22 year old Asian woman was diagnosed with pre-B acute lymphoblastic leukaemia (ALL). Her white cell count was 22.3 x 10^9/L, haemoglobin 8.8 g/L, platelets 27 x 10^9/L with blast count of 4.35. Her folate was within normal range. She was treated according to the UK ALL XII protocol. During induction she required intermittent courses of antibiotics for treatment of neutropenic fever. She experienced no side effects. In phase 2 of induction, after completion of intrathecal methotrexate she experienced no abnormality.

At presentation she was noted to have 3 cm hepatomegaly, which resolved within the first week of treatment. On day 26 of phase 2 of induction, after completion of intrathecal methotrexate at a total cumulative dose of 62.5 mg given over five courses, she complained of mild headache and difficulty finding words. Both symptoms were of sudden onset.

On examination, stuttering or staccato speech with mild expressive dysphasia were noted. Otherwise neurological examination was normal. There was a brief improvement followed by a further deterioration 24 hours later with progressive dysphasia, headache, behavioural disturbances (food refusal, crying, and refusing examination), and raised temperature, which never exceeded 38°C. No focal weakness, paraesthesiae, funal changes, or meningism were present. Reflexes and tone were normal. There appeared to be some truncal and limb ataxia, which was difficult to verify because of progressive behavioural disturbance. Dysphasia, which initially was only expressive, progressed to total aphasia. Tongue dyspraxia was noted. Dysphasia took the form of hesitancy, progressive stammer, and a progressive inability to complete words. There were no features indicative of a frontal lesion.

Computed tomography with intravenous contrast was performed showing normal anatomy. Magnetic resonance imaging (MRI) including T2 axial, T1 coronal and contrast T1 axial and coronal images, performed four days after the onset of symptoms showed no abnormalities. In particular there was no evidence of ischaemia, mass lesions, meningeal enhancement, or cortical signal abnormalities. Cerebrospinal fluid protein concentration was 0.29 g/L, glucose was 2.7 mmol/L, and microscopy showed no leukemic cells. Polymerase chain reactions for viral specific DNA performed on a cerebrospinal fluid sample, were negative for herpes simplex DNA, varicela zoster DNA, cytomegalovirus, enterovirus, herpes 6 DNA, and herpes 7 DNA. In view of the fever, acyclovir, amphotericin and broad spectrum antibiotics were given with initial lack of response.

Gradually her temperature settled with no impact on neurological symptoms. Gram negative bacilli were isolated from the Hickman line. In view of the persistence of behavioural and speech disturbance with paucity of neurological findings, a psychiatric opinion was sought. Assessment raised the possibility of mutism attributable to dissociative state or conversion disorder. Repeat MRI with MR venography and axial FLAIR images performed at 14 days was entirely normal. An EEG was performed showing excessive bilateral slow wave activity, suggestive of diffuse cerebral dysfunction compatible with diagnosis of infective, neoplastic, or metabolic encephalopathy.

We have found no evidence of leukaemia in the cerebrospinal fluid sample. Negativity of viral polymerase chain reactions and lack of response due to broad antiviral, antifungal, antibiotic treatment does not support the infective cause of the neurological symptoms. Metabolic causes were considered. Her electrolytes and folate were within normal ranges. Magnesium was low at 0.72 and was corrected. There was no renal or hepatic failure. She had not received high dose intravenous methotrexate. The diagnosis of methotrexate induced encephalopathy attributable to intrathecal methotrexate was made by exclusion.

DISCUSSION

Intrathecal methotrexate is important in management of ALL in prevention of recurrence in the central nervous system. Apart from its use in haematology and oncology the drug has also become one of the cornerstones of therapy of autoimmune conditions. Although pulmonary and hepatic toxicity are more common, damage to the nervous system is particularly worrying because of potentially significant disability. Its likelihood may be increased when methotrexate is used at high doses such as in treatment of ALL.

Neurotoxicity relating to use of methotrexate is well recognised. It has mostly been reported in children. We are not aware of any large studies of acute methotrexate neurotoxicity in the adult population. Massekeil and others reported acute tetraparesis and motoric aphasia with
images were normal. The T2 FLAIR MRI showed restrictive diffusion in frontoparietal white matter and splenium of corpus callosum. This case highlights the importance of diagnosis of methotrexate neurotoxicity in adult patients. Most cases reported so far (in children) have been on patients receiving oral or high dose regimens with leucovorin rescue. In this case only intrathecal therapy was administered. This case also illustrates the value of performing an EEG when MRI and computed tomographic findings are normal. Finally, the incomplete knowledge of a drug that has been in use for some 50 years is illustrated. With its increased use the mechanisms behind neurotoxicity need to be elucidated to maximise patient safety and reduce morbidity. Three months after completion of methotrexate, our patient was making a slow recovery. Mild ataxia was still present together with some expressive dysphasia, but she was able to converse. Full, spontaneous recovery from methotrexate toxicity is possible over a variable period of time.

CONCLUSIONS
This case highlights the importance of diagnosis of methotrexate neurotoxicity in adult patients. Most cases reported so far (in children) have been on patients receiving oral or high dose regimens with leucovorin rescue. In this case only intrathecal therapy was administered. This case also illustrates the value of performing an EEG when MRI and computed tomographic findings are normal. Finally, the incomplete knowledge of a drug that has been in use for some 50 years is illustrated. With its increased use the mechanisms behind neurotoxicity need to be elucidated to maximise patient safety and reduce morbidity. Three months after completion of methotrexate, our patient was making a slow recovery. Mild ataxia was still present together with some expressive dysphasia, but she was able to converse. Full, spontaneous recovery from methotrexate toxicity is possible over a variable period of time.

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