

Irreversible Methotrexate Induced Leukoencephalopathy Presenting as Recurrent Stroke like Episodes: A Case Report and Brief Literature Review

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ABSTRACT

A case of young female with leukemia on multiple chemotherapeutic agents including intrathecal methotrexate developed an attack of transient neurological deficit that improved spontaneously, followed by a second attack that was irreversible. MRI finding showed multiple area of increased signal intensity compatible with cytotoxic edema. These finding was suggestive of methotrexate induce toxic leukoencephalopathy. A critical decision was needed regarding discontinuing methotrexate from the chemotherapy protocol. The case is followed by a brief review about methotrexate induced leukoencephalopathy and the best way of its early detection and prevention.

Keywords

Methotrexate, Leukoencephalopathy, Diffusion weighted image, Stroke

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INTRODUCTION

Antineoplastic agents used to treat hematological malignancies are well known to induce neurotoxicity which can be acute or delayed months to year after completion of the therapy. Offending agents include methotrexate, L-asparaginase, vincristine and corticosteroid^[1].

The neurological manifestation can vary from mild personality changes and headache, to seizure, motor deficit or confusion and coma. The decision of the cause of these presentation is not straightforward and includes a wide differential diagnosis such as cerebrovascular accidents either hemorrhagic or infarction, cerebral venous thrombosis, central nervous system (CNS) metastasis, metabolic disturbances or direct toxic effect of the treatment. Linkage between the symptom onset and administration of certain anti-neoplastic agent in combination with radiological features of the insult, can help to determine the causative agents. This case discusses the methotrexate induced CNS toxicity, which has a predilection to white matter, especially in the periventricular area termed as leukoencephalopathy, and has a characteristic magnetic resonance imaging (MRI) abnormality which include increased signal intensity on diffusion weighted image^[1].

CASE

A 16-years-old right handed girl known to have acute lymphoblastic leukemia diagnosed 4 months before this

presentation. She presented with sudden onset of left side weakness and speech arrest after awakening from sleep. Her mother noticed personality changes and irritability during the week prior to her presentation. On further questioning her, she mentioned a similar attack 2 weeks ago. That attack was described by her mother as a sudden onset of dysarthria and right side weakness, which resolved spontaneously after few hours. When she was assessed at emergency department at that time, her neurological exam and computer tomography (CT) scan of the brain were both normal.

The patient was on her 8th week of consolidation chemotherapy protocol which includes: cyclophosphamide, vincristine, L-asparaginase and intrathecal cytarbine and methotrexate.

The patient was conscious, afebrile, no papilledema, no neck stiffness or other sign of meningitis. She was aphasic. Motor exam revealed left side weakness more in the upper limb with hyper tonicity and hyperreflexia. A brain CT scan was unremarkable except for an incidental finding of subarachnoid cyst. Lumbar puncture was done and it was normal with no blast cells. The patient was admitted with provisional diagnosis of acute stroke. MRI of the brain was done and showed multiple patchy ill-defined areas in deep white matter with high signal intensity areas in T2, Fluid-attenuation inversion recovery (FLAIR) and diffusion weighted images with no restricted diffusion per apparent diffusion coefficient (ADC) value. These finding

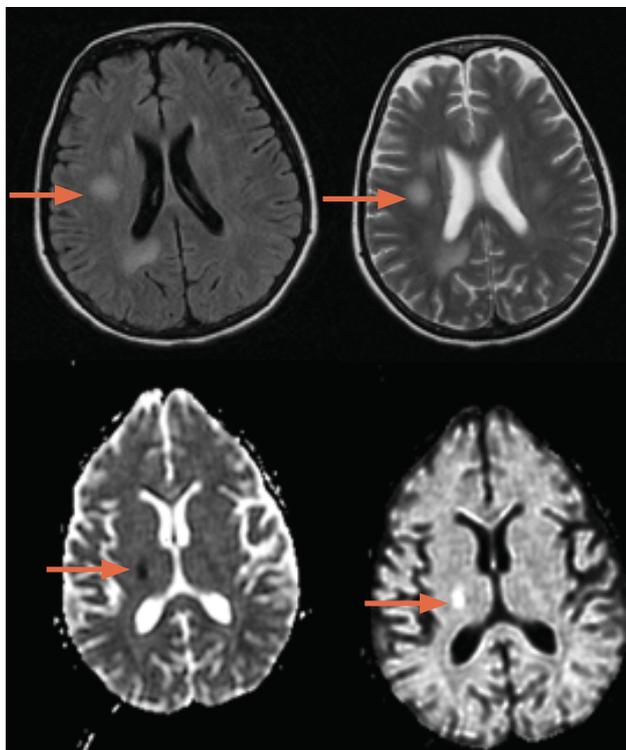


FIGURE 1. The first 2 images FLAIR, T2, respectively, showed patchy area of increased signal intensity in periventricular area representing leukoencephalopathy. The next 2 images ADC map and DWI, respectively, reveal area of restricted diffusion in right internal capsule representing ischemic stroke.

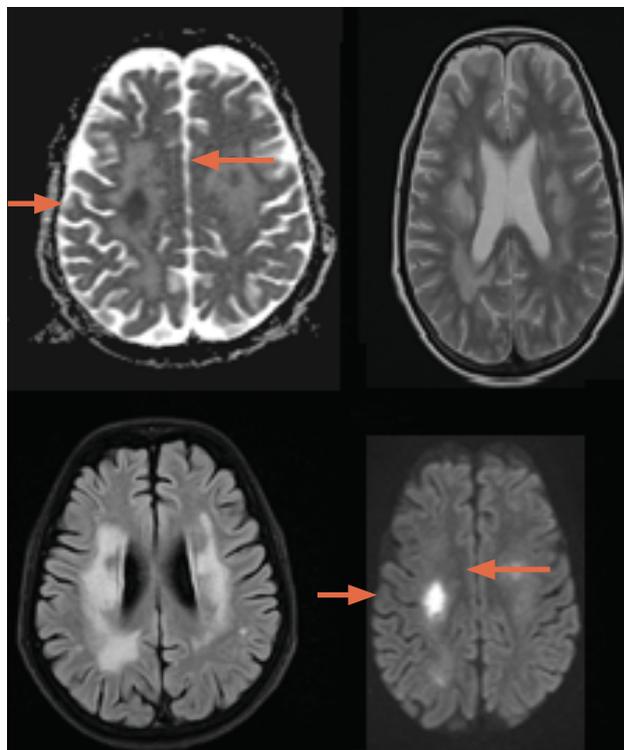


FIGURE 2. Follow up images that showed increasing signal intensities with more gliosis T2 and FLAIR; a recent ischemic changes in centrum semiovale (red arrows), first top images from left ADC map, T2, bottom from left FLAIR, DWI, respectively.

was representing white matter demyelination secondary to chemotherapy most likely methotrexate. However, some of these lesions were bright on diffusion-weighted imaging (DWI) with corresponding dark signal on ADC map consistent with acute infarction (Fig. 1).

A conclusion was made from the clinical picture and radiological features that the patient is suffering from acute toxic leukoencephalopathy, which is most likely attributed to methotrexate. A decision was made to hold further doses of methotrexate from the chemotherapy protocol. Leucovorin (reduced form of folic acid) was used as a rescue therapy to antagonize the toxic effect of methotrexate in addition to methylprednisolone. On a follow-up assessment, patient's mood and affect were improving as her speech returned to normal, but she sustained a residual right side weakness. Repeated MRI done 6 months later showed that the white matter changes is still present with more gliosis and there is evidence of recent ischemic changes in both centrum semi oval (Fig. 2).

DISCUSSION

Several chemotherapy drugs exert a selective (poorly understood) toxic effect on white matter and cause an acute or chronic diffuse or multifocal leukoencephalopathy^[2]. Methotrexate is the most common cause of chemotherapy induced leukoencephalopathy. This most often occurs in children given intrathecal methotrexate for treatment or prophylaxis of meningeal leukemia and in adults treated with high-dose IV methotrexate for primary CNS lymphoma^[2]. There is a spectrum of severity of methotrexate leukoencephalopathy. Some children or adults develop mild or moderate white matter signal abnormalities on MRI scans but have only minimal neurocognitive impairment. In children given intrathecal and IV methotrexate for leukemia, the MRI changes may actually improve over time^[2]. Other patients develop demonstrable neurocognitive deficits, generally not progressive, whose severity roughly correlates with the extent of white matter changes on MRI scans^[2]. As in this case, the patient had initially a reversible neurological deficit that improved within few hours, but this was followed later on by a second attack that was persistent. Acute toxic leukoencephalopathy with reduced diffusion may be clinically reversible and radiologically reversible on DWI, and may also be reversible, but to a lesser degree, on FLAIR MRI^[3]. However, in this case it was irreversible; this may be explained by the fact that the MRI initially didn't show abnormality only in the DWI, but also the FLAIR image showed abnormal signal intensity. In a study of 39 cases of acute toxic leukoencephalopathy and MRI abnormality, it was found that radiological reversibility is more common if the abnormality was in the DWI only^[3]. Therefore in this case, the reason of irreversibility may be because of the abnormality found on FLAIR images.

Although cases of methotrexate induced leukoencephalopathy is well reported in the literature, this paper was written to emphasize the importance

of recognizing this serious complication. Similarly, to point that the toxic effect of methotrexate is not always reversible, neither it is preventable by discounting the offending agent as many new lesion continue to appear in this patient despite holding the therapy for more than 6 months. Hence, based on the literature, the time frame for appearance of MTX-induced leukoencephalopathy ranges from immediately to 4 months after administration^[4].

The devastating complication encountered after administering methotrexate requires establishing guidelines for early detection of its toxic effect on the central nervous system. Until now, there is no well-established method for this. In the acute phase, CT scans or routine MRI scans (T1-weighted, T2-weighted, or FLAIR sequences) are usually normal, while diffusion weighted MR images show one or more focal areas of abnormally restricted diffusion in the centrum semiovale^[1]. Apparent diffusion coefficient (ADC) maps are suggestive of cytotoxic cerebral edema rather than focal ischemia. The lesions often do not respect vascular territories. Neurologic signs and symptoms resolve completely within several days without specific treatment. As in our case, the initial event that was reversible did not show any abnormality in the CT, but if MRI was performed at that time, it may have shown abnormality in the DWI.

Follow-up MRI scans in most patients show complete resolution of the diffusion abnormalities; some patients develop focal T2-weighted or FLAIR abnormalities in the previously seen areas of restricted diffusion^[2]. In one case series of 6 children with ALL treated with methotrexate and developed neurological complication, DWI demonstrated abnormal restriction of motion of water in the centrum semiovale in all six patients. This finding correlated to the acute onset of hemiparesis or aphasia. Fluid-attenuated inversion recovery (FLAIR) imaging was not positive at this time, but it was positive in all five patients in whom follow-up imaging was performed^[1]. Hence, we can conclude that DWI abnormality may be the first detected abnormality that alerts us to CNS toxicity. However, a larger study is needed to confirm the validity of DWI as a tool of early detection of CNS toxicity.

A worthy notice point is the controversy of the best rescue therapy. Option include high dose leucovorin^[5], aminophylline^[6], dextromethorphan^[7] and methylprednisolone each one act by different way on the methotrexate metabolism to prevent toxicity resulting from methotrexate action. The pathophysiology of methotrexate neurotoxicity is unclear. Several mechanisms has been proposed. These include increased adenosine accumulation, homocysteine elevation and its excitatory effects on the N-methyl-D-aspartate (NMDA) receptor^[7], and alterations of bipterin^[8] metabolism. However, until now, there is no head to head comparison to favor the use of one of these agents over other or the combination of these agents. In this case, the management plan was to hold further doses of methotrexate to prevent subsequent attacks. Intravenous methylpredensilone was administered, which mainly aimed to reduce inflammation and edema.

Another treatment strategy aimed to antagonize the effect of methotrexate. Thus, leucovorin that act by this mechanism was added. The patient responded to this treatment partially, which can be explained by the fact that some cytotoxic damage was established before adding the treatment; therefore, it could not be reversed.

CONCLUSION

Methotrexate is a widely used agent with a known neurotoxic effect. Early recognition of this complication and differentiating it from other neurological presentations is essential to prevent irreversible CNS damage. Although there is no gold standard method for diagnosis; DWI seems to be the best modality for early detection that can influence the decision to continue or hold the treatment. More studies are needed to evaluate the available agent used to reduce or reverse methotrexate induced leukoencephalopathy.

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اعتلال المادة البيضاء للدماغ نتيجة عقار الميثوتريكسات ظهر على هيئة سكتات دماغية متكررة، تقرير حالة ومراجعة موجزة للأدبيات

هند عبدالله النجاشي

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المستخلص:

وصف لحالة مريضة شابة تعاني من سرطان الدم، وتخضع لمعالجة كيميائية باستخدام عدد من الأدوية من بينها عقار الميثوتريكسات عن طريق الحقن داخل القراب، وقد عانت من نوبات عابرة و متكررة في قصور الوضائف العصبية، أدت الى اصابة مستديمه في الجهاز العصبي وقد أظهرت أشعة الرنين المغناطيسي زيادة في الاشارات الاشعاعية لبيضاء الدماغ في عدد من مناطقالدماغ، تؤكد وجود وذمة ناتجة عن تسمم للخلايا، و تشيرالنتائج الي تسبب الميثوتريكسات في إصابة ببيضاء الدماغ، وكانت هناك حاجة الى قرار حاسم لحذف علاج الميثوتريكسات من بروتكول المعالجة الكيميائية.

ويلي وصف الحالة ، مراجعة مختصرة لأدبيات حالات اصابةبيضاء الدماغ نتيجة استخدام عقار الميثوتريكسات، وأفضل الطرق للكشف المبكر والوقاية.