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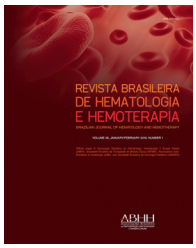

Case Report

Stroke-like encephalopathy following high-dose intravenous methotrexate in an adolescent with osteosarcoma: a case report

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Background

Methotrexate (MTX) is an important cytostatic drug in cancer chemotherapy and the most widely used antimetabolite in childhood cancers. It is effective in the treatment of acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma, histiocytosis and osteosarcoma. Although its mechanism of action is not fully understood, it had been postulated as a cell cycle specific folate that inhibits dihydrofolate reductase achieving elevated levels of homocysteine and excitatory amino acid neurotransmitter metabolites.

High dose MTX (HDMTX) is commonly used in the treatment of osteosarcoma.[1] It can cause acute, subacute and chronic neurological complications. Stroke-like encephalopathy is a sub-acute MTX neurotoxicity and a rare syndrome that manifests with an abrupt onset of focal neurological deficits.[2] It can cause hemiparesis, slurred speech, confusion, emotional lability, headache, choreoathetosis, and seizure.[1,3] The symptoms presented by children usually occur days to weeks after MTX administration and resolve over hours to days, without permanent neurological sequelae.[2,4]

We describe the neuroimaging features of a male teenage patient with osteosarcoma who presented with anxiety, confusion and emotional liability characterizing an episode of sub-acute transient cerebral dysfunction associated with alternating hemiparesis 12 days after receiving intravenous HDMTX (12 g/m^2). Imaging within 24 h of symptom onset showed bilateral symmetrical restricted diffusion involving white matter of the cerebral hemispheres. Computed tomography (CT), magnetic resonance imaging (MRI) and angiography showed no evidence of vasospasm or perfusion defects. MRI 30 days after first abnormality evidenced complete resolution and no signal was seen on T2 or fluid attenuated inversion recovery (FLAIR).

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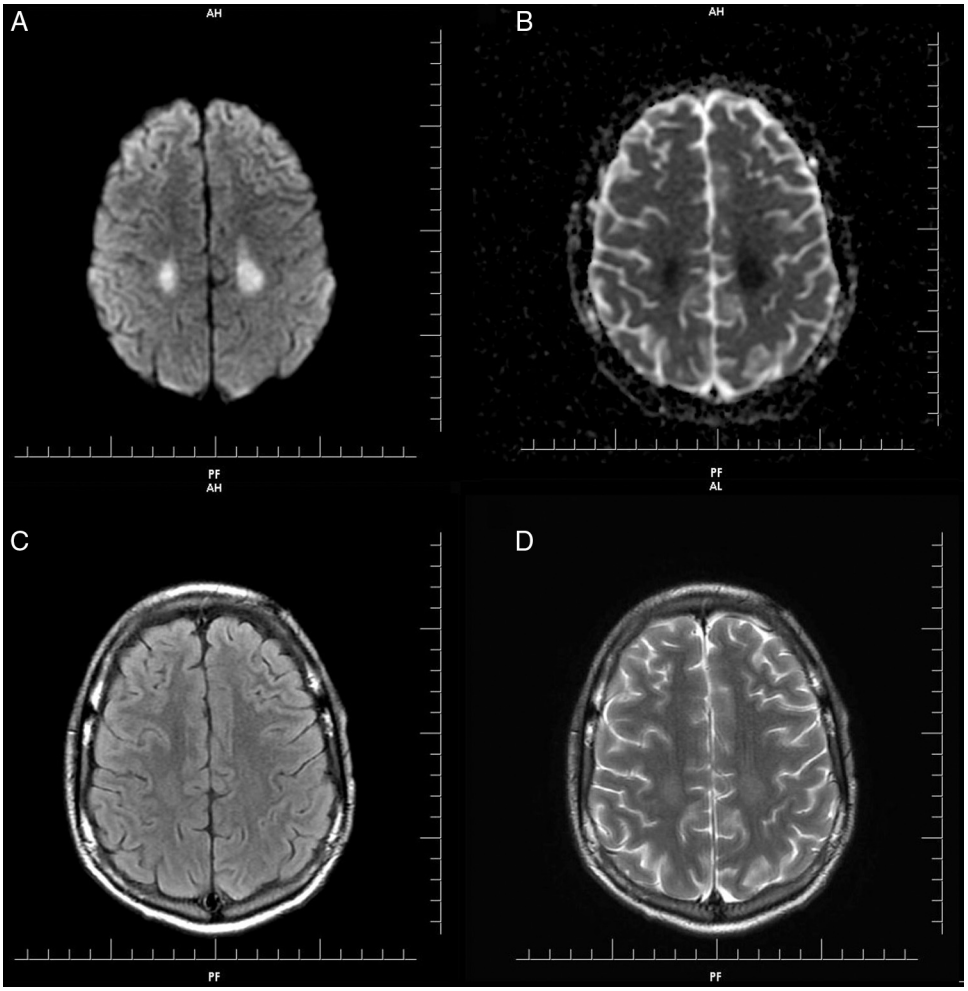

Figure 1 – (A) Diffusion weighted imaging (DWI): symmetrical hyperintense signal in parietal lobe white matter, neither cortical area nor deep gray matter structures were affected. (B) Decreased apparent diffusion coefficient (ADC): symmetrical hyperintense signal. (C) Axial T2/FLAIR image: discreet symmetrical hyperintense signal in parietal lobe white matter. (D) Axial T2: discreet symmetrical hyperintense signal in parietal lobe. No abnormality was observed in T1.

Case presentation

A 15-year-old boy diagnosed with osteosarcoma of the right distal tibia and pulmonary metastasis initiated neoadjuvant chemotherapy with cisplatin (60 mg/m^2/day for two days) and doxorrubicyn (37.5 mg/m^2/day for two days) alternating with HDMTX (12 g/m^2) in a six-week cycle. Leucovorin rescue (15 mg each six hours) was started 24 h after the end of every cycle of the HDMTX infusion until safe MTX plasma concentrations had been reached. Toxic levels were not observed.

The monitoring of MTX plasma levels after the fourth cycle showed concentrations of 6.26 μmol/L at 24 h, 0.78 μmol/L at 48 h and at 0.13 μmol/L at 72 h. Twelve days after this cycle, he presented psychomotor agitation, violent and bizarre behavior but preserved comprehension of time and space. His vital signs were stable. He was administered anxiety medications (clonazepam) and oxygen by facemask and the symptoms gradually resolved.

Subsequently, an abrupt onset of left-sided upper and lower limb paresthesia with ipsilateral hyporeflexia was observed without involvement of the face. An urgent brain CT scan did not show any evidence of vascular abnormalities to suggest vasospasm or hemorrhage. Additional hematological, viral serology, cerebrospinal fluid and blood chemistry (renal and liver functions and serum electrolytes) laboratory exams were performed with none identifying any abnormalities. Five hours after the beginning of neurological abnormalities, a physical examination of the patient was normal and there were no further complaints.

The following day, the patient complained of right-sided hemiparesis without reflexes of upper and lower limbs, but with mental status and vital signs being stable.

Gadolinium-enhanced MRI of the brain was performed and showed symmetrical hyperintense diffusion-weighted imaging (DWI) signals and decreased apparent diffusion coefficient (ADC) in the parietal lobe white matter, more prominent on the left side, however neither the cortical area nor deep gray matter structures were affected. There was no signal change on FLAIR and T2 images. No abnormality was observed in T1 images (Figure 1). Dynamic susceptibility perfusion imaging showed no evidence of abnormal mean transit time, cerebral