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Posterior reversible encephalopathy syndrome (PRES) induced by intrathecal methotrexate administration in a patient with acute lymphoblastic leukaemia

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ABSTRACT

A patient with B-cell precursor acute lymphoblastic leukaemia was diagnosed with posterior reversible encephalopathy syndrome (PRES) after an intrathecal administration of methotrexate during induction chemotherapy. PRES presented with headache, epilepsy, unconsciousness, blurred vision, hypertension, and vomiting. Also, characteristic lesions of the central nervous system were revealed by magnetic resonance imaging of the head, especially in the white matter of the posterior lobes.

Key words: chemotherapy, childhood, epilepsy, hypertension, magnetic resonance imaging

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Introduction

Posterior reversible encephalopathy syndrome (PRES) is a disease characterised by headaches, epileptic seizures, disorders of consciousness, arterial hypertension, and disturbances of vision [1, 2]. The symptoms are associated with vasogenic, reversible, focal brain oedema, mainly within the white matter. The lesions usually affect the posterior areas of the brain, the frontal lobes, cerebral cortex, and brainstem. With the application of magnetic resonance imaging (MRI), PRES is increasingly diagnosed as a complication accompanying the treatment of childhood cancers, especially secondary to acute lymphoblastic leukaemia (ALL) [3].

Case presentation

A 10-year-old patient diagnosed with ALL B-common, without initial CNS involvement, classified in the group of intermediate risk (IR), started induction chemotherapy according to the ALL IC BFM 2009 protocol. Two days after the first intrathecal administration of 12 mg of methotrexate (MTX), during prednisolone prephase (60 mg/m²) the patient complained about headaches, hypertension, vomiting, and loss of consciousness [4]. Following the administration of antiepileptic drugs (clonazepam, valproic acid), the boy remained mentally unresponsive, but with preserved reactions to pain stimuli and a sluggish pupillary response to light. An MRI scan revealed

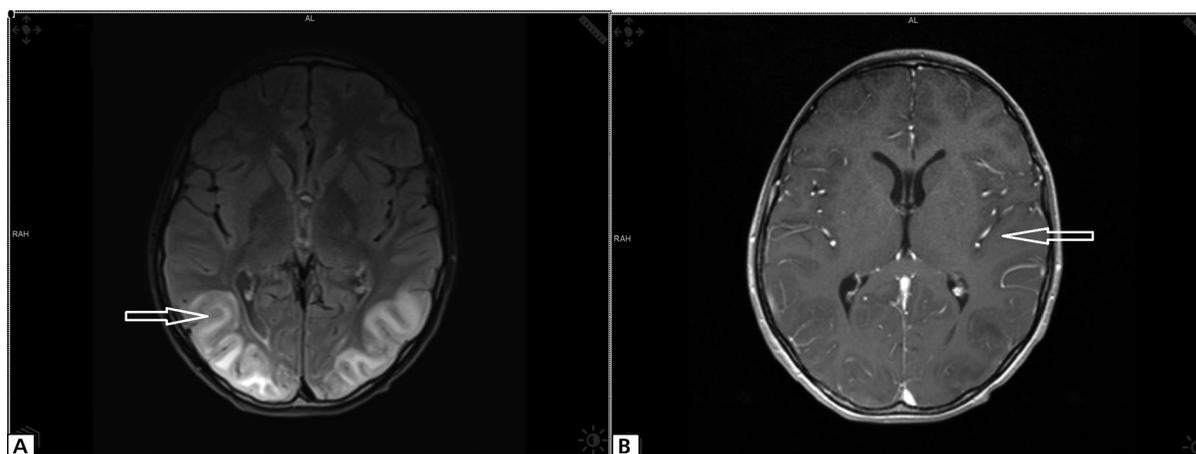


Figure 1. MRI examination (after the first PRES episode): axial scan, FLAIR sequence — hyperintense lesions in cortico-subcortical areas (A); axial scan, T1 sequence after a contrast an enhancement of subcortical white matter can be observed (B)

increased signal intensity on T2-weighted and FLAIR sequences in the cortical and subcortical regions of the occipital lobes, in the posterior temporal and parietal lobes and apical sections of the frontal lobes (particularly the left lobe) and within the cerebellar hemispheres. The areas showed discrete enhancement following contrast medium administration. The above MRI features were interpreted as oedematous/inflammatory lesions or encephalopathy secondary to ALL (Fig. 1).

During the days following the first epileptic seizure, the patient's hypertension persisted together with other symptoms including bradycardia, headaches, and vision disturbances (double vision, disturbances of colour vision, blurred near vision, "misty" vision, spots before the eyes). Furthermore, the patient experienced another seizure episode manifested as a focal epileptic event — tremor in the right leg. Five days after second dose of intrathecal administration of MTX (on day 12 of induction according to ALLIC-BFM 2009) and implementation of vincristine $1 \times 1 \text{ mg/m}^2/\text{day}$, daunorubicin $1 \times 30 \text{ mg/m}^2/\text{day}$, and L-asparaginase $5000 \text{ IU/m}^2/\text{day}$, the patient presented bilateral loss of vision. A subsequent computed tomography scan of the head revealed more prominent and slightly more extensive hypodense lesions, and an MRI scan showed an exacerbation of previously identified lesions.

Because of the patient's epileptic seizures, chemotherapy was postponed by six days after the first epileptic episode and by 11 days after the second ones. After the patient's general condition was stabilised, chemotherapy was continued from day 33 of treatment. Intrathecally administered MTX was replaced by cytarabine at a dose of 30 mg.

A follow-up MRI scan performed two months later demonstrated a marked regression of lesions manifest-

ing as a reduction of the extent of hyperintense areas within the cortical and subcortical regions of the occipital lobes, the posterior temporal and parietal lobes, and the apical sections of the frontal lobes. The areas were not enhanced after the contrast medium administration (Fig. 2).

Summary

Methotrexate is one of the main cytostatic drugs belonging to the class of antimetabolites used in the treatment of ALL. The neurotoxic activity of MTX can present as vomiting, disorders of consciousness, photophobia, and vision disturbances. MTX-induced neurotoxicity has been classified in the literature as sudden, acute/subacute, and chronic [5]. A similar temporal correlation between the time of the administration of MTX and the development of symptoms specific to PRES was observed in our patient.

The clinical and radiological features of PRES are non-specific, so other conditions must also be considered. It is necessary to rule out ischaemic stroke and intracranial haemorrhages which produce a range of radiological (CT) findings and clinical symptomatology similar to PRES. Consequently, establishing the final diagnosis requires an MRI scan to visualise hyperdense foci and densities of white matter. In uncertain cases, the decisive examination proving the diagnosis can be MRI angiography [3]. Depending on the location of lesions identified by MRI, PRES can be divided into several subtypes — with lesions in the occipital, frontal, parietal, and temporal lobes, and in the brainstem and cerebellum, dominated by vascular oedema in the frontal sulcus region, involving only the occipital and parietal lobes ("classic" PRES), and the most common variant, the so-called "asymmetric" PRES, with

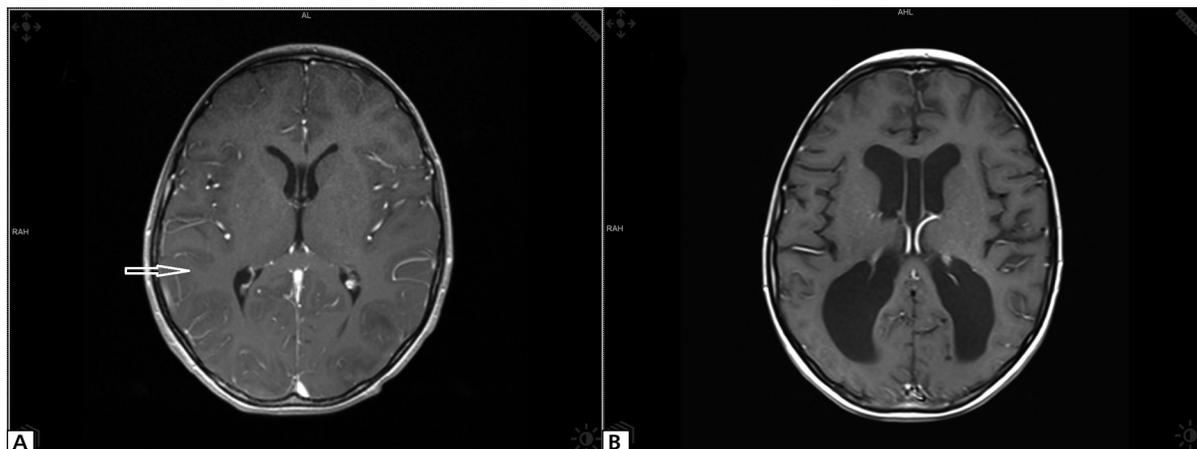


Figure 2. MRI examination (two months after the first PRES episode) — axial scan, FLAIR sequence — a slight hyperintense lesions of cortico-subcortical areas (A); axial scan, T1 sequence after contrast — no enhancement of subcortical white matter (B)

a partial combination of all the subtypes referred to above [3]. In the subtype presenting with brainstem and cerebellar oedema, the diagnostic process should always rule out brain herniation. A similar radiological manifestation also occurs in cases of cerebrovascular thrombosis and primary vasculitis. In addition, since the clinical picture of patients may create reasonable grounds to suspect meningitis, cytological and microbiological analysis of cerebrospinal fluid is necessary. Similar symptoms may occur in rare genetic diseases including CADASIL and MELAS syndromes, and may also accompany Creutzfeldt-Jakob disease, progressive multifocal leukoencephalopathy, or leukoaraiosis [3]. In the case of our patient, we performed differential diagnostics: blood and cerebrospinal laboratory tests, blood and cerebrospinal fluid culture was made, PCR tests for viral and microbiological infections to exclude neuroinfection and ALL involvement of the CNS, CT scans of the head to rule out stroke or haemorrhage, and as the next step MRI and eye examination was made. ALL of this research confirmed the diagnosis of PRES.

The treatment of PRES is largely limited to the management of symptoms. Patients with PRES are given anticonvulsants as well as hypotensive, antiedematous drugs and analgesics. The primary goal of therapy is to reduce the severity of syndromes. The patient described in the present study also received broad-spectrum antibiotic therapy and antiviral treatment due to preliminary

suspicion of neuroinfection. The need to continue the treatment of the underlying condition (ALL) in our patient necessitated a change in the therapeutic approach. To avoid toxicity induced by intrathecal administered MTX, the drug was replaced by another cytostatic — cytarabine and prednisone.

The continuation of treatment of ALL in accordance with the therapeutic regimen, as well as compliance with the time schedule, are also key prognostic factors for predicting the curing of ALL.

The authors declare no conflicts of interest.

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