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False-Photosensitivity and Transient Hemiparesis Following High-Dose Intravenous and Intrathecal Methotrexate for Treatment of Acute Lymphoblastic Leukemia

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Abstract

We describe a patient who was treated with high-dose intravenous and intrathecal methotrexate for acute lymphoblastic leukemia, and who manifested a false photosensitivity reaction with no prior evidence of sun exposure. This patient later experienced delayed transient hemiparesis following methotrexate administration, although without long-term sequelae. The etiology of these events is obscure, but suggestive of a vasculitic or immune-mediated reaction to methotrexate.

Keywords

acute lymphoblastic leukemia; encephalopathy; false photosensitivity; methotrexate

Introduction

Methotrexate is an integral component of the treatment for multiple childhood malignancies; its use is well tolerated when administered with hydration and alkalinization. Paroxysmal adverse effects, however, have been reported despite clinical supervision. Herein, we describe a patient who was treated for acute lymphoblastic leukemia with intrathecal and intravenous methotrexate and subsequently exhibited false photosensitivity and transient hemiparesis.

Case Report

A 17-year-old Caucasian male presented with a 2-month history of fatigue. Work-up revealed pancytopenia, with white cell count of 3,300/ μ L, hemoglobin of 9.3 g/dl, and platelet count of 64,000/mcl. He was diagnosed with high-risk B-precursor ALL, CNS stage 1. He was enrolled on COG Protocol AALL0232 with randomization to high-dose methotrexate during interim maintenance (IM). He tolerated induction therapy without complications and was a rapid early responder, without evidence of residual disease at day 29. He was advised to minimize sun exposure during therapy. He complied by wearing hats and limiting sun exposure to brief car rides and occasional outdoor activities in the late evening. His last outing prior to IM was brief, taking place ~1 week prior to therapy.

On day 1 of IM, the patient received 15 mg intrathecal methotrexate, 2 mg intravenous vincristine, and a 24-hr infusion of intravenous methotrexate (total dosage 5 g/m²). At the end of the infusion, he developed sunburn-like erythema, specifically on the sun-exposed surfaces of his arms, dorsal aspects of his fingers (Fig. 1A), and on the scalp below his hat border. Over the following week, this erythema desquamated consistent with a false photosensitivity reaction, resolving after 14 days.

Approximately 1 week after the first dose of methotrexate, he experienced right-sided hemiparesis, which lasted 30–60 min but resolved spontaneously. This event was not brought to the attention of the medical staff. He proceeded with the next cycle of methotrexate, with a 1-week delay, and the erythema returned with the same pattern (Fig. 1B).

The patient received the remainder of four cycles of methotrexate without complications, and drug clearance was prompt after each cycle. Eight days after the last doses of methotrexate, however, he had another 60-min period of spontaneously resolving right-sided weakness. Twenty-four hours later, the symptoms recurred with worsening right-sided hemiparesis and dysarthria, which again resolved spontaneously. Evaluation in the emergency department included a CT scan of the head that revealed no hemorrhage. He was admitted for observation; cranial MRI 2 days later showed restricted diffusion in the left corona radiata, mild hyperintensity in the right subcortical frontal white matter tract, but no evidence of acute ischemia or other white matter changes. MRA of the cerebral vessels was normal. CSF evaluation revealed normal protein, glucose, and leukocytes and was negative for CNS leukemia. He was discharged after 72 hr with no symptoms.

His subsequent dose of intrathecal methotrexate was held due to these acute events, but it was decided to continue his planned leukemia treatment, including later scheduled intrathecal methotrexate doses. Five weeks after the second hemiparetic event, the patient again received IT methotrexate without incident. One week later, he received his next dose of IT methotrexate, and 2 days later he experienced a *third* event of transient right-sided hemiparesis that resolved after 10 hr. Over the next 24 hr, his symptoms recurred, and broadened to bilateral hemiparesis, dysarthria, and lower facial nerve paralysis. Cranial MRI showed persistent subcortical white matter changes in the right frontal lobe (Fig. 2A), and new areas of restricted diffusion in the centrum semiovale bilaterally, with hyperintense signal on T2-FLAIR sequences (Fig. 2B,C). Over the following week, his symptoms fluctuated with eventual resolution after 3 weeks.

Further intrathecal chemotherapy was discontinued but he received other therapy per the COG protocol. He remains in remission at 9 months following his last event. He has no clinical sequelae from these events; follow-up brain MRI's at 1 and 6 months (Fig. 2D) show normalization of most abnormalities, although the hyperintense signal in the subcortical white matter persists.

Discussion

Methotrexate is an anti-mitotic agent that functions as an irreversible competitive inhibitor of folate synthesis. In pediatric oncology, it is commonly used as a high-dose infusion agent in combination chemotherapy for osteosarcoma, and in oral, intravenous, and intrathecal formulations for treatment of leukemia. Nephrotoxic side effects are most common but easily preventable with appropriate hydration and alkalinization, which prevents drug crystallization in the renal tubules [1].

Methotrexate is known for other adverse effects, with lower incidence yet significant morbidity. Dermatologic toxicity can vary from mild erythema to toxic epidermal necrolysis

[2]. Methotrexate is also linked to radiation recall and false photosensitivity. This phenomenon of sunburn-like erythema after methotrexate administration is well-described [3,4]. The mechanism of the skin sensitivity is unclear; it is distinct from true phototoxicity, as concomitant UV exposure does not worsen the reaction. It has been hypothesized that methotrexate might impair mononuclear cell response in sun-exposed tissues. Normally, the mononuclear cells quickly regulate and suppress inflammation due to UV exposure; impaired function by these cells allows prolonged inflammation. This can explain why the rash is seen only when methotrexate exposure is at a time removed from the original UV exposure [3]. Alternatively, there may be a type of small-vessel vasculitis, also described with methotrexate exposure [5,6].

Neurologic toxicities of methotrexate have been associated with both high-dose intravenous and intrathecal administration. These sequelae include irreversible morbidities such as leukoencephalopathy, but are more commonly transient effects such as seizures or brief hemiparesis [1,7,8]. Fifty percent of transient neuropathies present in 7–10 days after inciting drug exposure, often paroxysmally after multiple drug exposures [7,8]. Clinical work-up usually reveals no structural changes. Small case series, however, describe patients with hemiparesis and fronto-parietal MRI diffusion abnormalities, termed “transient leukoencephalopathy” [9,10]. These diffusion changes demonstrate localized edema, but the significance is unclear. Most patients had total spontaneous resolution of symptoms and were able to receive additional doses of methotrexate without recurrence.

Our patient demonstrates false photosensitivity with posterior reversible encephalopathy syndrome (PRES) following methotrexate administration. Although other drugs, including vincristine, were administered concurrently with methotrexate, no other drug was given consistently in a time frame that could have caused these symptoms, leaving methotrexate as the most likely cause. The recurrence of symptoms with repeat doses of methotrexate is noteworthy. These toxicities are consistent with a unique hyper-sensitivity to methotrexate in this patient; his initial false photo-sensitivity may have been a harbinger to his subsequent hemiparetic events. Skin symptoms were exacerbated by prior UV exposure, whereas in the CNS there was progressive sensitization with repeat dosing. Such effects were likely not specific to methotrexate since similar drug reactions have been described for other medications [11,12]. Furthermore, PRES is associated with autoimmune disorders [13], suggesting an immune-mediated methotrexate-associated vasculitis. This hypothesis is supported by his worsening symptoms with repeated exposures, and this also supports vasculitis as a possible cause of our patient's rash.

In summary, this case underscores the importance of advising patients to minimize sun exposure and maximize sunscreen protection in the time prior to and during methotrexate administration. We would also advise practitioners to monitor patients who show false photosensitivity for other adverse reactions and to monitor up to 2 weeks for adverse reactions after re-challenging with methotrexate. Finally, practitioners should strongly consider altering treatment plans to exclude IT methotrexate if neurological symptoms recur with re-treatment.

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Fig. 1.

A: Patient's right hand 24 hr following his second dose of IV methotrexate. **B:** Patient's right hand 7 days after a second dose of methotrexate, demonstrating worsening skin damage.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Fig. 2.

A: MRI T2/FLAIR image at day 2 of third hemiparetic event. Note the mild hyperintensity in right frontal subcortical white matter tract (green arrow). **B:** Diffusion weighted B0 image from day 2 of third hemiparetic event with mild hyperintensity in left corona radiata (blue arrows), and corresponding ADC-map image (**C**) with restricted diffusion (red arrows). **D:** T2/FLAIR sequence 1 month after third hemiparetic event. Note stable area of hyperintensity in R subcortical tracts. Diffusion-weighted signal did normalize at this time point. MRI at 6 months after the third hemiparetic event is unchanged (not shown). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]