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Case Report

An atypical presentation of ifosfamide-induced encephalopathy and its successful treatment with methylene blue: a case report

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ABSTRACT

Confusion remains a frequent event appearing during cancer course; many causes have to be excluded, including antitumoral agent-induced encephalopathy. Ifosfamide-induced encephalopathy is often underdiagnosed due to aspecific symptoms. The manifestations of this encephalopathy are usually moderate and spontaneously reversible but may also lead to coma and death. We describe symptoms of dysarthria and ataxia appearing following the second course of ifosfamide in a patient treated for sarcoma. Furthermore, methylene blue administration instantaneously reversed the process. This case report highlights an atypical presentation of encephalopathy induced by ifosfamide and the importance to consider methylene blue in this setting.

Introduction

Confusion remains a frequent event appearing during cancer course [1, 2]. Beyond cerebral bleeding, thrombosis and metastases, many cytotoxic agents cause encephalopathy episodes. Ifosfamide–induced encephalopathy is often underdiagnosed due to the poorly specific and spontaneously reversible symptoms; in some cases, however, symptoms are not easily manageable and become life-threatening, leading to coma and death [3-6]. Ifosfamide-induced encephalopathy is mainly diagnosed based on a neurological impairment in the absence of laboratory and radiological abnormality, and with close time relation with ifosfamide administration. Currently, no antidote is really approved for this drug-related toxicity. The main treatment is the discontinuation of the drug. The role of methylene blue remains to date unclear as no randomized clinical trial proved its effects. We report an atypical presentation of confusion and neurological disorders occuring after ifosfamide injection; furthermore, we also describe a rapid and drastic effect of methylene blue with a complete reversal of symptoms. We also review the mechanism of ifosfamide-induced encephalopathy and the rational for methylene blue administration [3] [7-10].

A 55-year old woman had a 10-year history of uterine sarcoma that initially required total hysterectomy and adjuvant radiotherapy. Six months ago, she developed recurrence with apparition of a right pelvic necrotic mass that was surgically removed. Pathology revealed a highly proliferative grade 3 endometrial stromal sarcoma. Two months ago, local recurrence caused obstructive renal insufficiency (creatinine value of 2,5mg/dl). The situation normalized after placement of a right nephrostomy. Creatinine decreased to its baseline value (1,7mg/dl). Due to previous radiotherapy and inability to perform margin free-surgery, chemotherapy regimen with ifosfamide-doxorubicine was decided

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(ifosfamide 3g/m² intravenous in 3 hours on day 1 and 2 and doxorubicine 30mg/m² intravenous in 30 minutes on day 1 and 2 with usual support medications including ondansetron, methylprednisolone, alizapride, uromitexan and methylene blue). A first course was administered during a 3-day hospitalization without any complication except moderate nausea. The patient was thus hospitalized for her second course of chemotherapy three weeks later. At admission, she had no complaint, clinical and neurological examinations were normal as well as hemodynamic parameters (blood pressure 140/70 mmHg, cardiac frequency 70 bpm). Laboratory tests were stable and unchanged, hemoglobin at 10.2 mg/dL with platelets and white cells in a normal range, normal coagulation, normal ionogram, normal liver enzymes and absence of inflammation. Creatinine remained stable at 1.6 mg/dl. Her medication only consisted of paracetamol 3g per day. The second course was administered, similarly to the previous one. Five hours after the end of the chemotherapy administration, on day two, the patient presented a loss of word, progressively associated with a degradation of her neurological functions; confusion rapidly worsened, as well as ataxia and dysarthria. She was unable to stand and stay up. There was no fever or neck stiffness; oculomotricity was normal, there was no focal sensory or motor deficit. The cardio-pulmonary examination was unchanged as well as the clinical parameters. There was no change in her medication, particularly in analgesics. Ionogram including natrium and calcium was normal, creatinine was decreased at 1.3mg/dL and there was no increased inflammation. Electroencephalogram was aspecific and did not reveal seizure manifestation. Cerebral magnetic resonance imagery (MRI) was normal and did not show any ischemic, bleeding or metastatic lesion. In front of the neurological degradation and suspecting a toxic reaction to ifosfamide, we rapidly started infusion of 1mg/kg methylene blue (50mg in 10 minutes) and intense hydration (2L/24h NaCl 0.9%). Two hours later, the patient completely recovered from her neurological troubles. A control MRI was performed one week later and exclude apparition of metastasis or athero-embolic event, confirming our hypothesis of ifosfamide-induced encephalopathy. Due to this toxicity, we did not complete the full course of ifosfamide-based chemotherapy.

Ifosfamide is an analog of cyclophosphamide, which is frequently used in a wide range of solid and hematologic malignancies. Ifosfamide is a pro-drug metabolized by the cytochrome P450 into an active drug (4-hydroxyifosfamide) that acts as an alkylating agent, leading to formation of DNA-DNA cross-links and resulting in DNA synthesis impairment and cell death. Common acute side effects of ifosfamide include nausea and vomiting, myelosuppression, alopecia and cardiac arrhythmia. Metabolism of ifosfamide also results in production of chloroacetaldehyde (CAA) and chloroethylamine, which is transformed by amine oxidase in CAA. Accumulation of CAA is responsible of encephalopathy; CAA penetrates the blood brain barrier and causes a rapid depletion of glutathione (GSH), reducing the neuronal cell defense against oxidative and nitrosative stress. Furthermore, it inhibits the processes implicated in mitochondrial respiration chain by inducing shift in the NAD: NADH ratio and by inhibiting Krebs cycle directly at the level of isocitrate formation [3, 7, 8].

Ifosfamide-induced encephalopathy has been reported in around 15-25% of treatments in retrospective studies and severity is mainly mild to moderate [3-5]. Manifestations are poorly specific and include delirium, visual and auditory hallucination, agitation, psychosis, cerebellar ataxia and can sometimes lead to seizure, coma and death [1, 2] [6, 9]. Encephalopathy occurs more frequently during the two first courses of ifosfamide-based chemotherapy and manifestations appear 12 to 146 hours (mean 46 hours) after starting of infusion. These neurological troubles seem dose-dependent and appear usually without any evidence of structural abnormalities in neurological imaging, although some studies describe electroencephalogram changes [10, 11]. Previous exposition to cisplatin, renal insufficiency, hepatic dysfunction, concomitant exposition to opioids, low hemoglobin or a low serum albumin may lead to a higher risk of encephalopathy [4, 5]. In our case, the only risk factor was the renal insufficiency that was however well controlled by correct hydration before ifosfamide administration.

These manifestations are usually spontaneously reversible when the administration is stopped rapidly, persisting for 1 to 12 days (mean 3 days). However, some manifestations persist despite the arrest of the agent, worsening and something resulting in coma and death [6, 9].

Treatment of encephalopathy is not standardized. Ifosfamide has to be discontinued immediately and patient has to be carefully monitored with neurological examination, adequate hydration and electrolyte correction. Methylene blue plays a role in encephalopathy treatment and prevention; by inhibiting amine oxydases, methylene blue reduces CAA formation, resulting in the restoration of the NAD: NADH ratio and in the Krebs cycle preservation [3-6] [9, 10]. Prophylactic use of methylene blue is known to reduce the incidence of encephalopathy during ifosfamide administration [12]. However, its role remains controversial in the treatment of encephalopathy as there is no randomized prospective clinical trial and as some case reports suggest only a moderate efficacy in reversing encephalopathy[11]. For our patient, only two hours after methylene blue administration, there was a complete resolution of symptoms, suggesting clear close relationship. This drastic effect is rarely described in literature but could highlight the importance to consider methylene blue rapidly when encephalopathy symptoms appear after ifosfamide infusion. Whether ifosfamide has to be continued in such situations remains unclear as there is no collected data registry. Despite our intention to follow the same regimen with decreased ifosfamide doses and increased methylene blue doses, the patient refused further ifosfamide regimen. Another chemotherapy combination was attempted without any clinical efficacy and disease progressed.

In conclusion, the main diagnosis criteria remain in one hand the neurological impairment in the absence of laboratory and radiological abnormality and in the other hand the close time relation with ifosfamide administration. There are no validated prospective data concerning the utility of methylene blue, but this case report suggests a rational to administer it rapidly in severe ifosfamide-induced encephalopathy.

Conflict of Interest

The authors declare no conflict of interest

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