Transient global amnesia associated with the infusion of DMSO-cryopreserved autologous peripheral blood stem cells

Dimethylsulfoxide (DMSO) is a solvent commonly used for the cryopreservation of autologous peripheral blood stem cells (APBSC). Side effects upon infusion of DMSO-cryopreserved APBSC mainly consist of nausea, emesis, chills, rigors, and cardiovascular events, such as bradyarrhythmia or hypotension. We report the case of a patient who received DMSO-cryopreserved APBSC after myeloablative chemotherapy for a relapsing lymphoma. The patient developed a rare reaction during the infusion manifesting as transient global amnesia. The clinical course during the reaction is described and an explanation of the possible causes is discussed. This observation underlines the need for an adequate DMSO depletion to limit neurotoxicity or other adverse manifestations.

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A 30-year-old man, diagnosed with Hodgkin's lymphoma, was admitted to our medical center for autologous peripheral blood stem cell transplantation. His history dates back to May 2006 when he presented with cervical, axillary and mediastinal lymphadenopathy associated with fever, chills, night sweats and weight loss. Pathological diagnosis was Hodgkin's lymphoma. The patient was treated with 6 cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) with complete remission in November 2006. He refused radiotherapy. His disease relapsed in February 2007. He received 3 cycles of ICE chemotherapy (ifosfamide, carboplatin, and etoposide) followed by stem cell collection and cryopreservation.

APBSC were prepared in the department of laboratory medicine following a standardized protocol. APBSC were collected, and the cell count was performed by flow cytometry. The cells were preserved in 10% DMSO/30% Plasmalyte A/22.5% autologous irradiated plasma and stored in liquid nitrogen.

The patient's pre-transplant evaluation was satisfactory. Salvage chemotherapy included high dose BEAM (carmustine, etoposide, cytarabin, melphalan) during which the patient had no complications. The infusion of APBSC was administered according to a predefined protocol. The patient received 8 mg dexamethasone intravenously 30 minutes prior to the infusion. The patient was transfused with 200 mL of stem cells ($CD34^+$ cell count = $7.55x10^6$/kg) over 15 minutes. This also included 20 mL of DMSO. Five minutes following the start of the infusion, the patient reported headache followed by chest tightness. Five minutes later he complained of numbness and stiffness of his right upper extremity that gradually worsened. At this point, the patient reported blurring of vision, became agitated and hyperventilating with a respiratory rate reaching 33/min. Two ampules of calcium gluconate were infused in 100 mL normal saline over 15 minutes. Arterial blood gases were taken and showed severe respiratory alkalosis with PH of 7.59, PaO_2 of 207 and $PaCO_2$ of 22. The patient was provided with a tight paper bag to breathe in and received 2 mg of intravenous midazolam for sedation. Subsequently, the patient appeared confused and kept reiterating the same questions over and over again. He was alert with a normal speech but disoriented to time and place. The episode lasted approximately four hours following which the patient was back to baseline with a normal neurological and mental status examination except that he had a complete amnesia of all the events that occurred during the period spanning from 2 hours preceding the infusion and until the end of his episode. Throughout the episode, his pulse oxymetry, ECG and blood pressure were normal. A brain MRI performed 5 hours after the end of the episode and an EEG were normal. A repeat MRI performed 24 hours later revealed an abnormal high signal on diffusion weighted sequences involving the right hippocampus (Figure 1a) with decreased apparent diffusion coefficient on ADC maps (Figure 1b). A diagnosis of TGA was made.

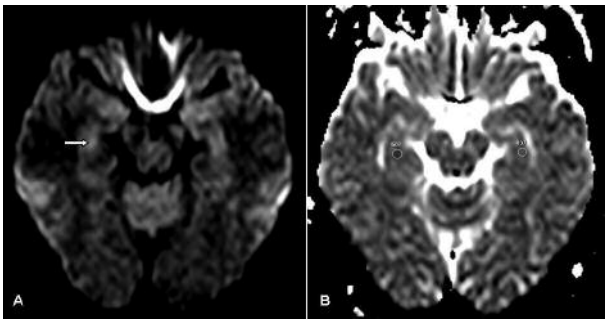

Figure 1. Axial diffusion weighted image (a) of the brain with the corresponding ADC map (b), obtained 29 hours following the episode of TGA, demonstrate high signal on diffusion in the right hippocampus (arrow) with low ADC. The ADC in the right hippocampus measures $0.681x10^{-3}$ mm²/s versus $0.837x10^{-3}$ mm²/s on the left side.

Our patient developed the typical manifestations of TGA following stem cell transfusion, including disorientation to time and place, the acute onset of anterograde amnesia manifested by asking the same questions repetitively, preservation of consciousness and retrograde amnesia of the whole event.[5] This diagnosis was further confirmed by a brain MRI that showed the typical MRI abnormality described in patients with TGA.[6] The temporal relationship between the infusion of cryopreserved stem cells and the episode of TGA suggests the

existence of a causal association between the infusion and the patient's symptoms. Although midazolam is known to produce anterograde amnesia independently of sedation,[7] it is highly unlikely to explain the clinical manifestations in this case for a number of reasons; the low dose of midazolam used in this case typically only produces partial anterograde amnesia and more importantly does not cause any retrograde amnesia.[8] In addition, the duration of the episode and the typical MRI findings strongly argue for a diagnosis of TGA.

Neurological complications following stem cell infusion have been rare. Only three of 179 consecutive patients experienced neurological complications during stem cell infusion.[9] Two of the patients suffered a cerebral infarction, while the third was presumed to have experienced an episode of TGA. The diagnosis was however uncertain and was only based on the fact that the patient had a retrograde amnesia for events spanning one week.

Despite the variety of proposed mechanisms for TGA, there is general agreement that the pathological changes affect the mediobasal temporal region, the hippocampus, and the parahippocampus.[10] In our patient, the episode of TGA could have resulted from a toxic effect of DMSO or as a secondary complication of hyperventilation. Favoring the possibility of a direct toxic effect is the finding that local infusion of DMSO can cause acute vasospasm in swine, a minority of whom also had microscopic histopathologic changes suggestive of angiotoxicity.[11] The other possibility is that the anxiety and hyperventilation induced by the infusion led to the TGA. Prior to the episode of TGA, our patient was quite anxious, hyperventilated and developed respiratory alkalosis. This could have resulted in alkalosis induced cerebral vasoconstriction with secondary ischemia in memory relevant structures.[12]

While the pathophysiology remains unclear, our case indicates that infusion of cryopreserved stem cell products may result in TGA. This observation underlines the need for reducing the concentration of DMSO or even depleting it before transfusion. Studies are needed to verify if these measures will limit neurotoxicity or other adverse manifestations of DMSO.

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