

Encephalopathy, stroke, and myocardial infarction with DMSO use in stem cell transplantation

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Abstract—Stem cell transplants are established therapy for hematologic and solid tumor malignancies. Known neurological complications of stem cell transplantation include CNS infection, seizures, strokes, metabolic encephalopathy, and hemorrhage. We report two cases of autologous stem cell transplantation complicated by cerebral infarction and myocardial injury. We postulate that the cryopreservative dimethyl sulfoxide may be responsible.

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Autologous and allogeneic stem cell transplants are established therapy for hematological and solid tumor malignancies. Currently, rates of transplantation are increasing, making complications of stem cell transplantation an important consideration. Here, we report two cases of autologous stem cell transplantation complicated by concurrent cerebral and myocardial infarctions and identify similar cases from the literature.

Case reports. *Case 1.* A 56-year-old man with mantle cell lymphoma became unresponsive at the end of a stem cell transfusion. He presented 9 months earlier with abdominal pain. He was found to have splenomegaly and diagnosed with stage IV mantle cell lymphoma with a circulating component. He received cyclophosphamide, adriamycin, vincristine, prednisone, and rituximab chemotherapy and achieved clinical remission. Five months afterward, he underwent autologous stem cell transplantation for consolidation. His stem cells were mobilized with cyclophosphamide and granulocyte-colony stimulating factor (G-CSF). Subsequently, he received cyclophosphamide, BCNU, and etoposide.

He had a history of gout. Home medications were allopurinol and ibuprofen. His admission examination was unremarkable. His admission lab values were notable for hematocrit 28.1%.

The patient received his stem cells in 10% DMSO (total volume 200 mL) IV through a single-cell filter. Toward the end of his infusion, he had headache. He then vomited and became unresponsive to noxious stimuli. He was intubated, although vital signs remained stable. Blood glucose, electrolytes, head CT, and EKG were unremarkable. That evening, he regained consciousness. He was extubated and found to have new neurologic abnormalities. He had dysarthria, a right facial droop, left facial thermanesthesia, and poor left-sided palatal elevation. His neurologic exam was otherwise unremarkable. He was alert and oriented, with intact language and attention. He recalled no chest pain. His total period of profound neurologic impairment was 12 hours.

Brain MRI revealed multiple acute strokes in the anterior and posterior circulations bilaterally (figure 1). MR angiography (MRA) of the head and neck was unremarkable. Blood cultures,

urine cultures, and chest radiographs were negative. Partial thromboplastin time (PTT) was 42 seconds; international normalized ratio (INR) was 1.1. Homocysteine, lupus anti-coagulant, anti-phospholipid antibodies, and hemoglobin A_{1c} were normal.

Cardiac enzymes rose with a troponin-I peak of 2.03 ng/mL (normal < 0.10). Limited echocardiography that day showed a depressed ejection fraction of 45%. Repeat transthoracic echocardiography 9 days later showed diffuse global hypokinesis/akinesis with an ejection fraction of 30%. No patent foramen ovale (PFO) was detected with agitated saline contrast. Cardiac catheterization 13 days after the event revealed no coronary disease; ventriculography estimated his ejection fraction at 60%.

At 6-week follow-up, he had good recovery with only mild right facial weakness.

Case 2. A 55-year-old woman with multiple myeloma complicated by chronic renal insufficiency became unresponsive after receiving stem cells in DMSO. Her past medical history was notable for relapsing–remitting multiple sclerosis with left arm and foot numbness. She was diagnosed with IgG lambda multiple myeloma 1.5 years prior to admission. Her disease was refractory to multiple chemotherapeutic regimens, and she elected to undergo autologous stem cell transplant. Her stem cells were mobilized with G-CSF in anticipation of high-dose melphalan, followed by stem cell rescue.

Home medications were allopurinol, escitalopram, and lorazepam. Admission exam was notable for chronic left hand numbness. Admission lab values were notable for blood urea nitrogen 39 mg/dL, creatinine 2.2 mg/dL, and hematocrit 25.7%.

The patient received her stem cells in 10% DMSO (total volume 500 mL). She tolerated the first day without complications. However, 15 minutes into her infusion the next day, she had severe abdominal pain. She was hypotensive to 77/53 mm Hg and mildly bradycardic. The transfusion was stopped; lorazepam 1 mg IV was given.

Ten minutes after completion of stem cell infusion, she again had abdominal pain, then spoke unintelligibly and flailed her extremities. She vomited and was fecally incontinent. She was unresponsive to noxious stimuli. She received flumazenil, with brief improvement, but remained unable to protect her airway, necessitating urgent intubation. Blood glucose, KUB, EKG, electrolytes, and noncontrast head CT were unremarkable.

Twenty minutes later, she recovered consciousness and was

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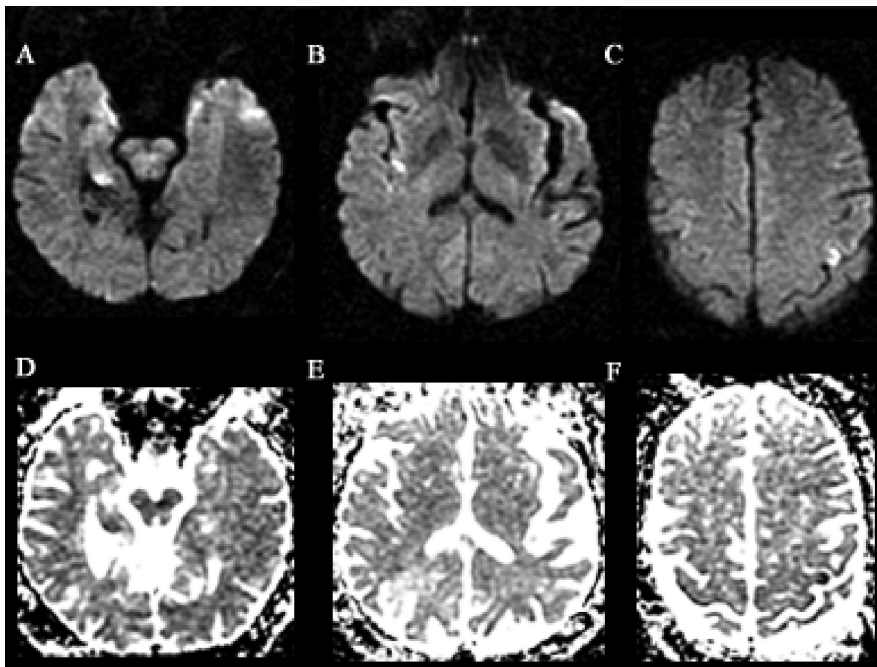


Figure 1. Patient 1. Twelve hours after acute neurologic decline, diffusion-weighted (top) and apparent diffusion coefficient (bottom) imaging revealed areas of restricted diffusion in the following locations: left midbrain and right entorhinal cortex (A and D); right insular cortex (B and E); left premotor cortex (C and F).

extubated. She was alert and oriented, with normal language and attention. The remainder of her exam was notable only for asterixis, bilateral sustained ankle clonus, and extensor responses to plantar stimulation. Her acute neurologic symptoms lasted for less than 1 hour total.

EEG showed diffuse slowing consistent with medication effect. Brain MRI that day revealed an acute stroke in the left anterior insular cortex (figure 2). MRA of the head and neck was unremarkable. Blood cultures, urine cultures, and chest X-ray were negative. PTT was 30 seconds; INR was 1.2. Aspartate transaminase (AST) rose slightly, peaking at 70 U/L. Liver function tests were otherwise unremarkable.

Cardiac enzymes rose with a troponin-I peak of 1.05 ng/mL at 9 hours after the episode. The next day, a transthoracic echocardiogram with agitated saline contrast showed a PFO with a small right-to-left shunt. The ejection fraction was 55 to 60%, with septal hypokinesia.

She recovered to her baseline neurologic status.

Discussion. These patients developed acute neurologic abnormalities immediately following infusion of

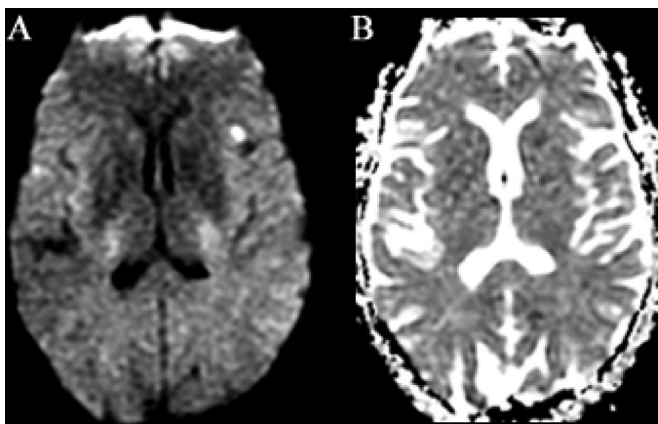


Figure 2. Patient 2. Ten hours after acute neurologic decline, diffusion-weighted (A) and apparent diffusion coefficient (B) imaging showed a lesion (probable ischemic stroke) at the junction of the left frontal lobe and anterior insular cortex.

stem cells suspended in the cryopreservative DMSO. Both patients had strokes, but the degree of encephalopathy was out of proportion to the burden of cerebral infarction seen on imaging. In addition, both patients suffered non-ST-elevation myocardial infarctions. In Patient 1, myocardial injury was severe enough to cause a reduced ejection fraction. However, no atherosclerotic epicardial coronary disease was seen on cardiac catheterization. Rather, the pattern of hypokinesia and akinesia seen on echocardiography, with return to baseline within 2 weeks, suggests stress cardiomyopathy.

The etiology of the strokes is unclear. Patient 1 had small infarctions in multiple vascular territories, arguing for either a diffuse process or a cardioembolic source. Patient 2 had one small infarction, with a PFO seen on echocardiography. Neurologic complications of stem cell transplantation have been reported (table).¹⁻⁵ In most cases, cerebral infarction associated with stem cell transplantation has been attributed to paradoxical stem cell embolus, with a right-to-left intracardiac shunt.^{3,4}

In addition, the troponin-I rose in both patients over hours after the events. Although uncommon, PFO with paradoxical embolus may cause myocardial infarction via occlusion of cardiac microvasculature, with coronary arteries remaining patent.

Although paradoxical embolus could explain cerebral and myocardial injury in Patient 2, the use of a single-cell filter and absence of PFO in Patient 1 argue for another mechanism for concurrent cerebral and myocardial infarctions.

One possibility is that the cerebral infarctions led to myocardial injury through sympathovagal dysregulation. This phenomenon has been described with infarctions of the insular cortex, believed to

Table Summary of neurologic complications of stem cell transplantation

Patient	Age, y	Sex	Diagnosis	Volume, mL	% DMSO	Neurologic	Onset	PFO	Ref.
1	56	M	Mantle cell lymphoma	200	10	Multifocal infarction	Immed	No	Current
2	55	F	Myeloma	500	10	Left frontal lobe infarction	10 min	Yes	Current
3	59	M	Myeloma	928	10	TGA (normal MRI)	8 h	N/R	2
4	53	F	NHL	157	10	Right frontal hemorrhage	2 h	N/R	2
5	49	M	Amyloidosis	297	10	Multifocal infarct/Aspergillosis	Immed	N/R	2
6	10	F	AML	300	N/R	Multifocal infarction	Immed	Yes	3
7	62	M	Hodgkin lymphoma	220	10	TIA (normal MRI)	Immed	Yes	4
8	55	F	Myeloma	400	10	Multifocal infarction	Hours	N/R	5

All patients reported to have neurologic events after infusion of cryopreserved stem cells, including current cases. Of note, Cases 3, 4, and 5 did not have obvious ischemic events and may have different mechanisms of injury.

DMSO = dimethyl sulfoxide; PFO = patent foramen ovale; TGA = transient global amnesia; NHL = non-Hodgkin lymphoma; AML = acute myelogenous leukemia.

function in autonomic regulation.⁶ Both patients had insular strokes.

Alternatively, the encephalopathy, myocardial injury, and cerebral infarctions could be the result of a single agent. Encephalopathy similar to our patients' has been seen with infusions of DMSO even when the cryopreservative is given in isolation.^{7,8} Moreover, in a swine model, arterial infusion of DMSO alone caused dose-dependent acute vasospasm in 23 of 24 subjects.⁹ Finally, a retrospective, survey-based study suggests that decreasing DMSO concentration may decrease overall toxicity as well, with toxicity rates of 1.5% for subjects given 10% DMSO vs 0.3% for lesser concentrations.¹⁰ DMSO toxicity—via diffuse vasospasm or another mechanism—may explain our patients' symptoms.

Some have advocated the ultrafiltration of stem cells or PFO closure to prevent cerebrovascular complications of stem cell transplantation.^{3,4} This would be helpful if PFO with paradoxical embolus were the sole cause of strokes associated with stem cell transplantation. However, we were unable to detect a PFO in Patient 1, who received ultrafiltered stem cells.

In the cases presented here, the stem cell–DMSO infusions were associated with a transient, profound encephalopathy. This encephalopathy, with concurrent cardiac and gastrointestinal effects, is suggestive of acute DMSO-induced systemic toxicity.

Although 10% DMSO is a standard carrier for stem cells, alternative agents or a lesser concentration of DMSO may be safer and equally effective. Although a cryopreservative is obligatory for autologous stem cell transplants, allogeneic transplants may avoid this toxic exposure entirely by using freshly harvested cells whenever possible.

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