Neurotoxicity from intrathecal gadolinium administration

Case presentation and brief review

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Several water-soluble gadolinium chelates are used intravenously as contrast media for MRI, particularly when there is suspicion of neoplasm, infection, or inflammatory disease, and in some cases of MR angiography. Recent reports of neurologic symptoms in patients with repeated exposure to intravenous gadolinium-based contrast¹ and growing evidence that intravenous gadolinium is deposited in brain parenchyma² have fueled concerns over the safety of intravenous gadolinium-based contrast.

Recent studies have also assessed the usefulness of intrathecal gadolinium (IT-Gad), administered in low doses, for various indications, including localization of CSF leaks.³ While the short-term tolerability of low-dose IT-Gad appears good, long-term safety data are lacking and formal IT-Gad dosing guidelines do not exist. Furthermore, case reports of inadvertent high-dose IT-Gad highlight the potential for severe neurotoxicity.

Herein, we describe the clinical course of a patient who developed medication-refractory status epilepticus after accidental administration of high-dose IT-Gad and summarize the clinical features and outcomes of similar cases.

Case

A 55-year-old man, who presented to our hospital for cervical myelography, was mistakenly administered 12 mL of gadobutrol intrathecally. Within minutes, the patient developed nausea and emesis, became nonverbal, and developed convulsive seizures, eventually becoming apneic and cyanotic. His initial examination (following lorazepam, levetiracetam, fosphenytoin, and trendelenburg positioning) showed hemodynamic instability and coma with normal pupillary/corneal reflexes but absent cold caloric, gag/cough, and deep tendon reflexes. Generalized seizures remitted only with anesthetic doses of pentobarbital, and attempts to wean the patient from a burst suppression pattern on EEG were unsuccessful because of re-emergent electrographic seizures arising from anterior temporal regions bilaterally, despite the use of 3 antiepileptic drugs and methylprednisolone. Discontinuation of pentobarbital without recurrent status epilepticus was possible only on day 9. While brainstem reflexes normalized within 12 hours of exposure, he did not regain consciousness until day 11 and examination at that time showed encephalopathy as well as diffuse weakness and areflexia, which improved gradually over the course of 3 weeks.

His initial head CT showed diffuse contrast enhancement of the subarachnoid, cisternal, and intraventricular compartments. MR imaging on day 8 also showed the diffuse subarachnoid and cisternal contrast enhancement, clearance of intraventricular contrast, and restricted diffusion of the hippocampi, likely from prolonged status epilepticus. Repeat MR imaging (day 23) showed resolution of hippocampal cytotoxic edema and clearance of contrast from the

PRACTICAL IMPLICATIONS

Intrathecal administration of gadolinium may result in catastrophic neurologic injury. Policies that prevent accidental injection of high-dose intrathecal gadolinium should be advocated.

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(A) Coronal noncontrast head CT completed at the time of symptom onset, showing contrast enhancement in the subarachnoid, cisternal, and intraventricular compartments. (B) Coronal MRI T1 sequence completed on day 8, showing diffuse subarachnoid, cisternal, and parenchymal contrast enhancement and clearance of intraventricular contrast. (C) Axial diffusion sequence completed on day 8, showing restricted diffusion of the hippocampi, likely from prolonged status epilepticus. (D) Coronal MRI T1 sequence completed on day 23, showing clearance of subarachnoid, cisternal, and intraventricular contrast, but diffuse cortical enhancement from parenchymal deposition of gadolinium. The cortex is usually darker than subcortical white matter on T1 sequences (inlay E) and is reversed in this case because of gadolinium staining.

subarachnoid, cisternal, and intraventricular spaces, but diffuse cortical enhancement from parenchymal deposition of gadolinium (figure for imaging).

When last assessed, 25 weeks after exposure, seizures had not recurred and encephalopathy had improved, but severe anterograde memory deficits persisted. On the Montreal Cognitive Assessment (MoCA), his score was 9/30 when tested 3 weeks following symptom onset, and the MoCA improved to 22/30 at last follow-up (table e-1, [links.lww.com/CPJ/A111](https://www.aaanet.org/CPJ/A111) for full scoring).

Discussion

Gadolinium encephalopathy is a potentially catastrophic complication of high-dose IT-Gad. A few similar cases have been reported (table for summary). Common presenting symptoms are vomiting (likely from chemoreceptor trigger

zone stimulation) and seizure, as occurred in our patient, but encephalopathy without seizure, ataxia, visual changes, and muscle stiffening are also described. How IT-Gad disrupts neurologic function is not known, but in vitro laboratory studies have suggested that gadolinium induces oxidative stress and alters intracellular Ca^{2+} stores in neural tissues.⁴

Because of the lack of adequate trials of IT-Gad administration, there is no gadolinium contrast medium that is approved for intrathecal use at any dose. Nonetheless, IT-Gad has been administered off-label to several hundred patients in the course of formal studies and otherwise.⁵ In these studies, different brands of contrast media were used but the IT-Gad dose generally ranged from 0.1 to 1.0 mL, much less than the 12 mL that was inadvertently administered to our patient. Severe neurotoxicity was not observed, but even low-dose IT-Gad precipitated nausea in 6 of 95 and vomiting in 2 of 95 patients in one larger prospective study.³ Furthermore, one patient suffered transient global amnesia following a 1 mL dose of gadobutrol,⁶

Table Symptoms and outcomes following exposure to high-dose IT-Gad

Case	IT-Gad dosage and reason for injection	Clinical notes	Follow-up and outcome
Present report	12 mL of gadobutrol for cervical myelography	55-year-old man with vomiting followed by medication-refractory status epilepticus. Diffuse weakness on regaining consciousness. Treated with steroids and antiepileptics.	25-wk follow-up, anterograde memory deficits
Reference 8	Product and dose not reported but given for assessment of an intrathecal pain pump	56-year-old man with expressive aphasia and memory deficits	6-d follow-up, full recovery
Reference 9	2 mL of gadobutrol for assessment of an intrathecal pain pump	60-year-old woman with severe leg pain and spasm responsive to intravenous midazolam.	26-wk follow-up, full recovery
Reference 10	8 mL (4 mL + 4 mL–3 h apart) of gadodiamide for lumbar epidural steroid injection and subsequent epidural blood patch	61-year-old woman with 2 convulsive seizures followed by coma. Intubated for 9 d.	6-mo follow-up, normal neurologic examination, but possible focal onset seizures controlled with phenytoin
Reference 11	6 mL of gadopentetate dimeglumine for lumbar myelography	42-year-old man with aphasia and vomiting, followed by muscle rigidity, seizure, and depressed level of consciousness	1-y follow-up, visual disturbances, and bilateral optic atrophy
Reference 12	10 mL of gadobutrol for a lumbar imaging study	53-year-old woman severe pain followed by medication-refractory status epilepticus	2-mo follow-up, noted to be improving with residual deficits that were not specified
Reference 13	15 mL of gadopentetate dimeglumine for myelography	34-year-old woman who developed vomiting, headache, and generalized seizure and coma. Treated with lumbar drain and steroids. Regained consciousness after 8 d.	8-mo follow-up, full recovery
Reference 14	20 mL of gadopentetate dimeglumine for cervical myelography	64-year-old man with vomiting, blurred vision, ataxia, and somnolence and delirium. Treated with steroids.	8-wk follow-up with mild ataxia and concentration difficulties

Abbreviation: IT-Gad = intrathecal gadolinium.

a symptom closely linked to temporal lobe pathology. Given that high-dose IT-Gad caused vomiting and temporal lobe seizures in our patient, the side effects reported with lower doses in some studies may represent low-grade neurotoxicity, and future work using IT-Gad should include a formal assessment of neurologic effects. We believe that our patient's persistent cognitive deficits, particularly his anterograde amnesia, are attributable to hippocampal injury from prolonged seizures,⁷ but a direct cytotoxic effect of IT-Gad cannot be excluded.

The best management practices for IT-Gad-related neurotoxicity are unknown. CSF lavage has been suggested as therapeutic option and may be reasonable given the potential for severe morbidity. Outcome data following gadolinium encephalopathy are sparse. Imaging data suggest that the gadolinium deposition in brain tissue may be permanent, resulting in a characteristic reversal of the signal intensity of the cortex relative to white matter on T1 MRI sequences (figure). Policies that prevent accidental injection of high-dose IT-Gad should be advocated.

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