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Case Report

Gadolinium Encephalopathy After Intrathecal Gadolinium Injection

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Background: Gadolinium-induced encephalopathy is a well documented complication due to the inadvertent entrance of a high dose of gadolinium into the intrathecal compartment. In lab animals, injecting gadolinium into the intrathecal compartment resulted in neurotoxicity and seizures. It is also well recognized that the presence of autologous blood in the intrathecal compartment can cause a broad range of neurological changes that can include seizures and mental status changes. At the time of writing this report, there were no references in the literature of simultaneous injection of gadolinium and blood into the subarachnoid space.

Case: We present a case of a patient who received a high dose of gadolinium in the epidural space for needle placement confirmation during a fluoroscopically-guided epidural steroid injection for the treatment of lumbar radiculopathy. The injection was complicated by a wet tap necessitating an epidural blood patch for post-dural puncture headache. Shortly after the injection of the autologous blood, the patient developed grand-mal seizures and mental status changes requiring endotracheal intubation and admission to an intensive care unit. We describe the clinical course and management, as well as brain MRI findings and cerebrospinal fluid (CSF) changes. The patient made a complete recovery and was discharged.

Conclusion: This case reinforces the need for using a low dose of gadolinium for the confirmation of needle placement in the epidural space, especially in procedures that carry the risk of inadvertent intrathecal injection. We attribute these findings to inadvertent simultaneous intrathecal injection of high dose gadolinium and autologous blood. A literature review of the cases of gadolinium-induced encephalopathy is provided followed by discussion.

Key words: Postdural puncture headache, epidural blood patch, intrathecal gadolinium, seizures, mental status changes, encephalopathy

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A 61-year-old Caucasian female with a history of chronic lumbar radiculopathy and right lower extremity radicular pain received an epidural steroid injection (ESI) at a community-based outpatient pain clinic. The first attempt was executed at the L4-L5 interspace using a 15 cm epidural needle (gauge unknown) under fluoroscopic guidance utilizing loss-of-resistance technique. It was complicated by a "wet tap," and the needle was subsequently withdrawn. A second attempt at the L5-S1 interspace was successful. Due to a documented history of iodine allergy, a total of 4 mL [1,148 mg gadodiamide (287 mg/ml gadodiamide)] of non-iodine containing contrast, gadolinium (Omniscan), was injected into the epidural space, which was confirmed on an epidurogram in biplanar views. A 9 mL solution containing 2 mL/80mg of Depo-Medrol diluted in 7 mL of preservative-free normal saline (presumably for better spread) was

injected into the epidural space incrementally while periodic negative aspirations were performed. The patient was observed while still at the clinic and seemed to have tolerated the procedure well. There were no immediate complications.

Approximately 30 minutes post-ESI, while still being observed at the clinic, the patient developed a postdural puncture headache of 7-8/10 intensity when sitting up. She did not report fever or chills, had a negative neurological exam, and no meningeal signs were present. Within minutes, she received conservative treatment with an IV fluid bolus, which failed to provide relief. Nearly 3 hours later, while still at the clinic, an epidural blood patch (EBP) was performed using a 19-gauge 9-cm Tuohy needle introduced at the L5-S1 interspace. A second dose of 4 mL of gadolinium was injected into the epidural space. After obtaining an adequate epidurogram in biplanar views again, a total of 15 mL of autologous blood was injectedin an incremental manner. The patient tolerated the procedure well and the headache diminished considerably immediately after the procedure.

While recovering at the clinic after the EBP, the patient developed mental status changes and was witnessed having a grand-mal seizure. Subsequently, she was transferred to the same community-based outside hospital's emergency department where her seizure resolved spontaneously just prior to arrival. However, she was found to be unresponsive to verbal or noxious stimuli. A computed tomography (CT) scan of the head was suspicious of a subarachnoid hemorrhage versus gadolinium collection in the subarachnoid space. Following the CT, the patient had a second grand-mal seizure which lasted several seconds. At that point, she was successfully treated with one gram of fosphenytoin sodium although she remained unresponsive.

The patient was then transferred to our tertiary care university hospital for further management, as the outside hospital did not have an adequate level of critical care services required for the patient. During transit, she developed respiratory distress and required endotracheal intubation. She was quickly weaned off mechanical ventilation and extubated on the first day of admission. The initial labs revealed a basic metabolic profile remarkable for hyperglycemia, negative troponins/cardiac enzymes, an electrocardiogram displaying sinus tachycardia, and arterial blood gas results that showed mild respiratory acidosis with compensatory metabolic alkalosis. The magnetic resonance imaging (MRI) evaluation of the brain was limited secondary to artifact related to the presence of gadolinium and therefore was non-diagnostic (Fig. 1). An MRI of the spine was not conducted. A chest x-ray revealed pulmonary vascular congestion, atelectasis, and bilateral pleural effusions; CT scans of her head and abdomen were also inconclusive secondary to patient movement, as she was significantly agitated. On day #2 of admission, the patient was reintubated secondary to worsening respiratory distress and agitation, despite generous sedation with midazolam, lorazepam, and haloperidol. She remained intubated and sedated with midazolam and fentanyl, which was later switched to propofol and dexmedetomidine to allow for quicker weaning. She also received levetiracetam, magnesium sulfate, and methylprednisolone for cerebral protection.

On day #3, pan-cultures were sent off due to concerns that she might be developing an infectious complication since the patient had an elevated white blood cell count and questionable aspiration pneumonia based on her chest X-ray. She was started on empiric antibiotic coverage with vancomycin and piperacillin. On day #4, bronchial cultures revealed Streptococcus Pneumoniae along with a corroborating chest X-ray indicating right lower lobe pneumonia.

On day #5, a diagnostic lumbar puncture was successfully and atraumatically carried out with a 25-gauge Quincke needle at the L3-L4 level. Interestingly, the cerebrospinal fluid (CSF) had a turbid red tinge that minimally decreased from the first to the fourth tube. Each tube consisted of 2 mL of CSF. Remarkably, within seconds after filling each vial, the CSF appeared to precipitate into a gelatinous consistency. CSF cultures were negative, while cell counts revealed nucleated cells 33, red blood cells >10,000/μL, neutrophils 88, lymphocytes 11, and eosinophils 1. However, these counts were deemed questionable secondary to clotted CSF sample. The CSF protein level was 423 (normal: 12-60mg/dL), and lactate dehydrogenase was 364.

On days #6 and #7, there was no significant clinical improvement. The patient remained intubated and sedated, with periodic neurologic checks. She was afebrile and was continued on her antibiotic regimen. Serial chest x-rays showed that her pneumonia was resolving. A repeat brain MRI without contrast revealed hyperintensity areas in the subarachnoid space and the ventricles on FLAIR/T1-weighted images, which were attributed likely secondary to artifact (Fig. 2). A final CT scan of the head on day #8 after admission revealed no acute intracranial process, but did show the presence of chronic ethmoid and sphenoid sinusitis (Fig. 3).

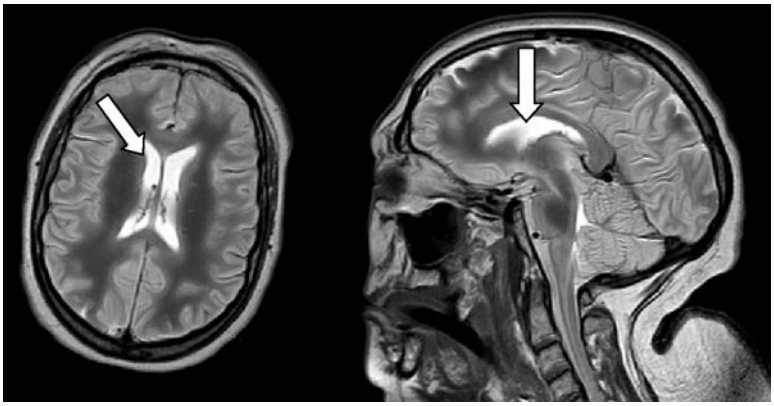

Fig. 1. *T1 weighted transverse and sagittal MRI images showing intraventricular and intracerebral gadolinium accumulation on day of admission.*

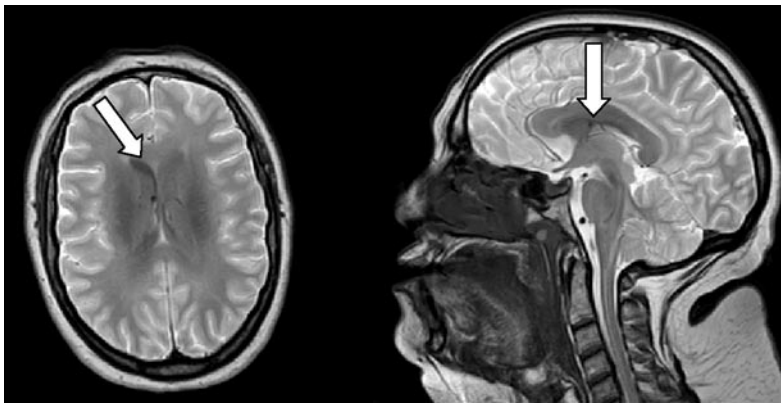

Fig. 2. *T1 weighted transverse and sagittal MRI images showing decreased intraventricular and intracerebral gadolinium accumulation on day #2.*

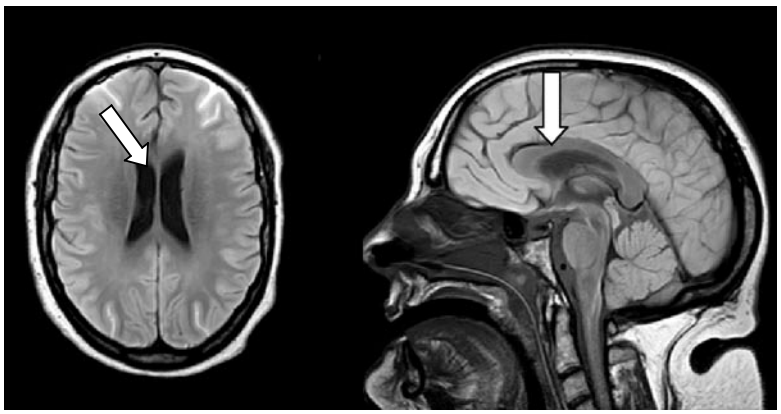

Fig. 3. *T1 weighted transverse and sagittal MRI images showing nearly resolved intraventricular and intracerebral gadolinium accumulation on day #6.*

Also on day #8, the patient started to follow verbal commands, and her pulmonary function started to improve significantly as evaluated by both clinical signs and arterial blood gas data. After a brief continuous positive airway pressure (CPAP) trial, the patient was extubated on day #9. She suffered no functional deficits post-extuabation, and was amnestic towards the entire event. She was discharged home on day #10.

She is currently followed by our neurology outpatient clinic. Having come twice for follow-up appointments over the last 6 months since being discharged, the patient has had negative neurological exams, but has reported having questionable intermittent partial seizure-like activity, which is being controlled with phenytoin.

Discussion

We report a case of high-dose intrathecal gadolinium administration resulting in seizures, altered mental status, and respiratory distress. Gadolinium-related encephalopathy was initially used to describe a 57 year-old female with end stage renal disease, who developed an encephalopathic syndrome after repeated intravenous gadolinium-enhanced MR imaging (1). Although gadolinium chelates are relatively safe, hypersensitivity reactions and systemic toxicity have been seen to occur with extracellular distribution and markedly decreased renal clearance. Neurotoxicity has been estimated at approximately 1% on initial studies, and it has been attributed to gadolinium's pharmacokinetics (2).

In 2007, a similar case involving a 64-year-old female without renal failure, who inadvertently received 20 mL of intrathecal gadolinium dimeglumine (10 mmol), resulting in ataxia and delirium, was reported (3). Other similar cases have involved 2 patients having grand-mal seizures requiring intensive care unit care after accidental intrathecal administration of gadolinium for cervical discograms confirmed on MRI. However, considering that both these procedures happened within one hour of each other in the same clinic, to a very experienced radiologist using the same batch of gadolinium, a possibility that the batch was somehow defective could not be excluded. In this study, there was also one patient who received 3 mL of gadolinium intrathecally for an attempted interlaminar epidural injection at the L5-S1 level; the procedure ended up being converted to a transforaminal injection. That patient was discharged without complications (4).

There are studies showing the relative safety and reliability of using low-dose intrathecal gadolinium for MRI in which 0.5-1.0 mL gadolinium dimeglumine (0.25-0.5 mmol Gd) had been administered into the subarachnoid space and were reported to be well tolerated with minor adverse effects (e.g. headache) and only rare severe, but transient complications like hemiparesis and gait disturbance (5). In our case, the dosage was several times that the typical amount, likely explaining the severity and prolonged signs and symptoms of encephalopathy.

In our patient, a working diagnosis of gadolinium encephalopathy was ultimately made because no other causes of the patient's encephalopathy were immediately discovered. Infectious meningitis and subarachnoid hemorrhage (SAH) were high on our differential diagnosis. The patient's short clinical course and CSF findings did not support infectious origins. In regards to SAH, the MRI and CT images showed a unique gravity-based high density distribution, which did not support intrathecal bleeding. In addition, the radiological studies did not exhibit the dynamic density change pattern normally expected with SAH. However, we speculate that the lumbar puncture revealing xanthochromia and an abnormal consistency could be a result of the additional volume of autologous blood that entered the intrathecal space via the existing dural defect during the epidural blood patch. The complications of EBP are few, mild, and transient. Local complications include leakage of blood into subcutaneous tissues, cauda equina syndrome, subdural hematoma, back and radicular pain (from the mass effect of the injected blood), and epidural infection. The literature describes a diverse group of complications following EBP including bradycardia, loss of consciousness, seizures, deterioration of mental status, cerebral ischemia (possibly due to vasospasm), recurrent headache (alternative pathology should be considered), neck pain, vertigo, dizziness, tinnitus, ataxia, and facial nerve palsy. Acutely increased CSF pressure might be the cause of some of these. Major complications or persistent neurological deficits are rare (6). Since gadolinium and blood can have the same appearance on MRI images, it is possible that the gadolinium was masking blood from the blood patch that was also present in the intrathecal space. Although the loss of resistance technique, without gadolinium, can also be utilized for epidural injection, imaging guidance to direct the needle and to confirm epidural needle placement can improve the accuracy of medication delivery (7-9). Conversely, even though the intrathecal spread of the depot form of methylprednisolone (Depo-Medrol) could have contributed to clinical symptoms presented, we do not believe that the steroid

injection itself played an active and essential role in the pathogenesis of the clinical picture. In a study where methylprednisone was injected in 89 patients suffering from neuropathic pain due to post-herpetic neuralgia, there were no neurologic complications (10). This notion is also supported by a pilot study in which intrathecal administration of betamethasone was administered to 13 patients for the treatment of metastasis-related pain (11). There were no neurologic complications reported including seizures.

The CSF sample did have a turbid red tinge, which we speculate was related to the epidural blood patch. Likely, the epidural spread of gadolinium during both injections entered the subarachnoid compartment via the previous dural puncture site. Based on CSF changes, we believe that the blood intended for the epidural space entered the subarachnoid space and made the clinical picture of gadolinium toxicity even more severe. Conversely, it might have caused a transitory vasospasm which could explain the mental status changes and seizures. To our knowledge this is the first case describing the simultaneous accidental administration of a high dose of gadolinium and autologous blood intrathecally.

There is minimal literature regarding the use of gadolinium based contrast agent in the intrathecal space, as there are limited clinical applications (12). In the few series published thus far, which corroborate our findings, low-dose intrathecal gadolinium based contrast agent [0.5-1.0 mL gadolinium dimeglumine (0.25-0.5 mmol Gd)] has not been associated with any significant adverse effects (5). However, relatively higher doses, such as was accidentally used in this case, can cause neurotoxicity primarily affecting oligodendroglial and astroglial cells, which has been shown in animal models (13,14). Taking into account our findings, we recommend using small dose gadolinium injections for the confirmation of epidural space and choosing an interspace one or 2 levels caudad from the one that was associated with the dural puncture.

Conclusion

Confirmation of the placement of the needle in the epidural space is especially important in patients who have abnormal anatomy of the spine on one hand, and on the other hand require a precise placement of the autologous blood patch for the treatment of postdural puncture headache. In this case report we describe a patient whose management was confounded by the history of allergic reaction to iodine based contrast dye. A gadolinium based contrast was used instead to confirm the epidural placement which followed by the injection of the autologous blood. We believe that the ensuing encephalopathy occurred due to inadvertent simultaneous entry of gadolinium and blood into the subarachnoid space. This case emphasizes the importance of using the smallest amount of gadolinium based contrast in the epidural space, especially in the presence of a dural puncture.

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