

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Neurotoxic manifestations of high-dose intrathecal gadolinium administration for CT myelogram ☆☆☆

Pannaga Malalur, MD^{a,b,*}, Peter C. Rajacic, MD^{a,c}

^a Department of Internal Medicine, University of Nevada Las Vegas, 1707 W Charleston Blvd, Ste 230, Las Vegas, NV 89012, USA

^b Division of Oncology, Ohio State University, Columbus, OH

^c Internal Medicine, Dedicated Senior Medical Center, ChenMed, Philadelphia, PA

ARTICLE INFO

Article history:

Received 19 May 2020

Revised 28 July 2020

Accepted 28 July 2020

Keywords:

Intrathecal
Gadolinium
Myelogram
Neurotoxicity
Off-label

ABSTRACT

Use of intrathecal gadolinium for contrast-enhanced myelography and cisternography remains off-label and is currently not FDA-approved. We report a 70-year-old male who underwent CT myelogram utilizing off-label high-dose intrathecal gadolinium who developed altered mental status and bilateral hearing loss. Workup ruled out meningitis (infectious and aseptic), infectious encephalopathy, encephalitis, and hypothyroidism. MRI of the brain and lumbar spine without contrast displayed fluid collection in L4-5 interspace and diffuse cerebrospinal fluid (CSF) hyperdensity consistent with intrathecal gadolinium. The patient eventually improved with high-dose IV dexamethasone and supportive care and resolution of diffuse CSF hyperdensity was observed on repeat MRI. There are limited data demonstrating the safety of low-dose intrathecal gadolinium due to which usage remains off-label. Our case highlights the need for caution when using substances for off-label indications and reinforces the usage of less invasive and noninvasive diagnostic modalities when possible.

© 2020 The Authors. Published by Elsevier Inc. on behalf of University of Washington.

This is an open access article under the CC BY-NC-ND license.

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Background

A small but growing body of literature exists regarding use of intrathecal gadolinium for contrast-enhanced myelography and cisternography [1]. Limited data demonstrate the safety of utilizing low doses (0.5–1 cc) [2–4]. There are rare case reports of neurotoxic effects involving high doses of intrathecal gadolinium, all inadvertently administered [5–8]. Use of

intrathecal gadolinium for MR myelography and cisternography remains off-label [9].

Case details

A 70-year-old Caucasian male with a prior history of multiple lumbar spinal surgeries and documented anaphylactic

☆ Competing interests: None.

☆☆ Authors' present affiliations are different from where work was conducted. All work was done under Department of Internal Medicine, University of Nevada Las Vegas.

* Corresponding author.

E-mail address: Pannaga.malalur@osumc.edu (P. Malalur).

<https://doi.org/10.1016/j.radcr.2020.07.084>

1930-0433/© 2020 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

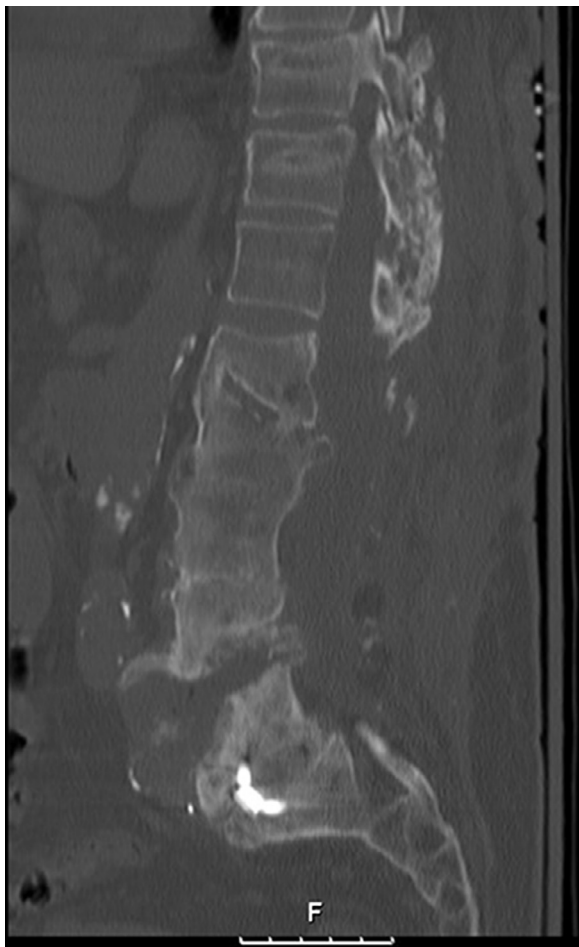


Fig. 1 – CT L-spine without contrast demonstrating extensive postsurgical spinal and paraspinal deformity and anterior interbody spacer at L5-S1.

reaction to iodinated contrast obtained imaging at an outside center for progressive back pain. The outside imaging facility, due to erroneous assumption of presence of extensive spinal hardware, decided that MRI was not an option. Due to this unique situation in a patient who could not receive iodinated contrast or undergo MRI, the facility opted to perform CT myelogram with intrathecal gadolinium though this procedure was highly unusual for them. The patient provided informed consent for this off-label procedure.

Intrathecal gadopentetate dimeglumine, Gd-DTPA (Magnevist), was administered at an intentional dose of 12 cc without dilution as per the outside imaging center report; no complications occurred during the procedure. Several hours later, he developed abrupt bilateral hearing loss followed by progressively worsening altered mental status. He was initially evaluated at a local emergency room where basic laboratory studies and a CT head displayed no abnormalities. He was transferred to our hospital for neurology specialty care.

Upon arrival, he was notably somnolent and confused, had significantly decreased hearing bilaterally, was afebrile with normal vital signs, had free movement of all extremities with no nuchal rigidity, and an otherwise unremarkable exam.

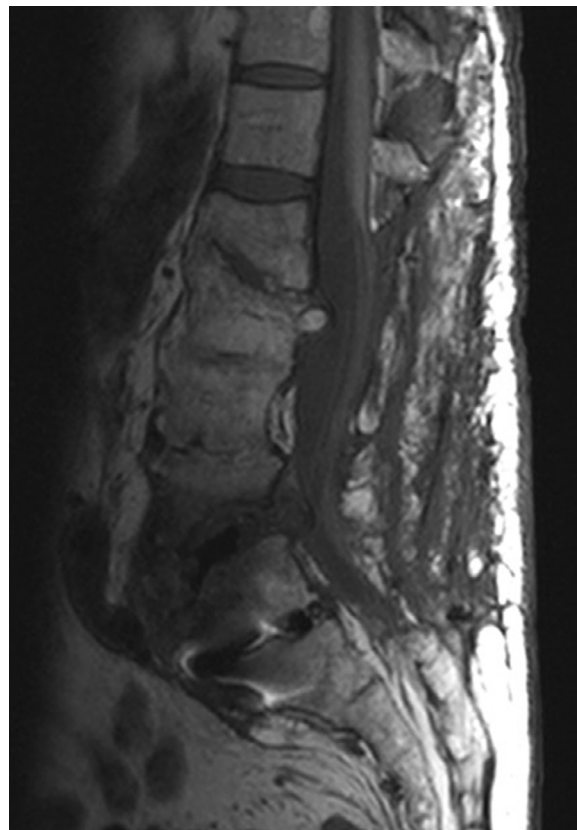


Fig. 2 – MRI L-spine without contrast showing fluid collection in L4-5 region and diffuse CSF hyperdensity from intrathecal gadolinium.

Routine laboratory tests, infectious serologies, cultures, and CT imaging of brain and spine did not show acute changes (Fig. 1). L spine CT only an L5-S1 interbody spacer as posterior hardware had been previously removed. Lumbar puncture was normal except for elevated protein of 124 mg/dL (reference range 15-60 mg/dL). MRI of the brain and lumbar spine without contrast displayed fluid collection in L4-5 interspace at the intrathecal injection site and diffuse cerebrospinal fluid (CSF) hyperdensity consistent with intrathecal gadolinium (Fig. 2).

The patient eventually returned to baseline with high-dose intravenous IV dexamethasone and supportive care. By day 2, he was awake and oriented to place and person. Confusion improved steadily and resolved completely by day 5. Repeat LP on day 4 demonstrated decline in CSF protein to 80 mg/dL. Resolution of diffuse CSF hyperdensity and L4-5 fluid collection was observed on repeat MRI performed on day 4. Bilateral hearing loss had improved significantly, but not completely resolved, at time of discharge on day 6.

Discussion

Intrathecal administration of gadolinium currently represents an off-label use; wider clinical utilization is limited by lack

of experience, paucity of data, and concerns about adverse outcomes [9]. Clinical applications are primarily restricted to neuroimaging and include needle tip positioning for image-guided spine procedures (nerve blocks, spine diskograms, epidural injections) and CE-MR cisternography and myelography for evaluation of hydrocephalus, cranial and spinal CSF leaks and flow dynamics, ventricle obstruction, and neurosurgical planning [1].

Dose-dependent neurotoxicity and neuropathologic changes of intrathecal gadolinium were demonstrated in rats in 1996. About 5 $\mu\text{mol/g}$ brain was the lowest dose noted to produce changes. Behavioral and morphologic changes were not seen below 3.3 $\mu\text{mol/g}$ brain [10].

The first human pilot study using intrathecal gadolinium was performed by Zeng et al. [2]. Eleven patients received a single dose of Gd-DTPA of either 0.2 mL (0.07 $\mu\text{mol/g}$ brain), 0.5 mL (0.17 $\mu\text{mol/g}$ brain), or 1 mL (0.36 $\mu\text{mol/g}$ brain). None of the patients exhibited neurologic symptoms or behavioral changes. This established the potential for clinical applications of intrathecal gadolinium [2]. In comparison, our patient received approximately 4.3 $\mu\text{mol/g}$ brain.

A large multicenter study by involving 95 patients showed that low-dose intrathecal gadolinium (0.5–1 mL) was safe [3]. Aydin et al. documented the long-term safety over a 5-year follow-up period in 51 patients given 0.5 mL Gd-DTPA for evaluation of CSF rhinorrhea [4].

Rare case reports exist linking neurotoxic effects (headache, vomiting, confusion, seizures, respiratory depression) to inadvertent administration of high doses (ranging from 5–15 mL) of intrathecal gadolinium [5–8]. Recommended treatment for patients with such neurotoxic manifestations is unclear. IV steroids and continuous CSF drainage have been suggested as possible treatment [5]. Our patient improved with high-dose IV steroids and fluids; continuous CSF drainage was not required. Adverse event was reported to manufacturer.

Each mL of Magnevist contains 469.01 mg gadopentetate dimeglumine salt, which amounts to a total of 5628.12 mg gadolinium in this patient who received 12 cc [11]. Our patient underwent the off-label CT myelogram with high-dose intrathecal gadolinium administration as the outside imaging center erroneously presumed presence of extensive spinal hardware (due to his surgical history). Interestingly, L spine CT at our facility revealed that he did not, in fact, have significant spinal hardware; only an L5–S1 interbody spacer was present as posterior hardware from prior spinal surgeries has been previously removed. This is an important learning point for clinicians to obtain detailed medical and surgical history from patients, and not to make assumptions based on reported history alone. Our patient would likely have reported the removal of posterior spinal hardware to the outside facility if questioned in detail. Also, if he had undergone a baseline CT without contrast first, he would have been able to obtain routine MRI with IV gadolinium, avoiding the aforementioned off-label procedure and resulting toxicity.

The ionicity of contrast is closely related to osmolality. (Gadobutrol [Gadavist] is an exception; although nonionic has high osmolality.) Gd-DTPA (Magnevist), an ionic contrast agent, has a high osmolality of 1960 mOsm/kg which is hy-

per tonic compared to normal serum osmolality which ranges 285–295 mOsm/kg. Peripheral IV administration, particularly rapid injection of higher doses, has been associated with toxicities related to hypertonicity including transient cardiodepression, nephrotoxicity in patients with advanced renal disease, and skin toxicity from contrast extravasation. Routine peripheral IV administration has minimal implications for a systemic osmolar effect as even the most ionic gadolinium agents result in a minimal increase in serum osmolality (0.5%–1.5%). However, high doses administered intrathecally can result in significant osmolar effect resulting in neurotoxicity from osmolar overload [12,13].

Conclusion

A small collection of studies have evidenced the safety of low dose (0.5–1 cc) intrathecal gadolinium, but due to overall paucity of data, safety has not been fully established, dosing guidelines do not exist, and use for MR cisternography/myelography remains off-label [1–4,9]. Supportive measures with IV fluids, IV steroids, and CSF drainage appear beneficial in managing neurotoxic adverse effects [5].

This case highlights the need for caution when using substances for off-label indications and reinforces the usage of less invasive diagnostic modalities when possible. Patients who cannot use iodinated contrast or undergo MRI studies, such as our patient, would benefit from development of protocols to minimize procedural risk. Testing levels of serum and CSF gadolinium to ascertain clinical or prognostic correlation could be a potential area for further research.

REFERENCES

- [1] Algin O, Turkbey B. Intrathecal gadolinium-enhanced MR cisternography: a comprehensive review. *AJNR Am J Neuroradiol* 2013;34:14–22.
- [2] Zeng Q, Xiong L, Jinkins JR, et al. Intrathecal gadolinium-enhanced MR myelography and cisternography: a pilot study in human patients. *AJR Am J Roentgenol* 1999;173:1109–15.
- [3] Tali TE, Ercan N, Krumina G, Rudwan M, Mironov A, Zheng QY, et al. Intrathecal gadolinium (gadopentetate dimeglumine) enhanced magnetic resonance myelography and cisternography: results of a multicenter study. *Invest Radiol* 2002;37:152–9.
- [4] Aydin K, Terzibasoglu E, Sencer S, Sencer A, Suoglu Y, Karasu A, et al. Localization of cerebrospinal fluid leaks by gadolinium-enhanced magnetic resonance cisternography: a 5-year single-center experience. *Neurosurgery* 2008;62:584–9.
- [5] Li L, Gao FQ, Zhang B, Luo BN, Yang ZY, Zhao J. Overdosage of intrathecal gadolinium and neurological response. *Clin Radiol* 2008;63:1063–8.
- [6] Calvo N, Jamil M, Feldman S, Shah A, Nauman F, Ferrara J. Neurotoxicity from intrathecal gadolinium administration case presentation and brief review. *Neurol Clin Pract* 2020;10(1):1–4.
- [7] Park KW, Im SB, Kim BT, Hwang SC, Park JS, Shin WH. Neurotoxic manifestations of an overdose intrathecal injection of gadopentetate dimeglumine. *J Korean Med Sci* 2010;25(3):505–8 (published correction 25(4):656).

-
- [8] Provenzano DA, Pellis Z, DeRiggi L. Fatal gadolinium-induced encephalopathy following accidental intrathecal administration: a case report and a comprehensive evidence-based review. *Reg Anesth Pain Med* 2019;44:721–7299.
- [9] ACR-ASNR-SPR Practice parameter for the performance of myelography and cisternography. Revised 2019 (Resolution 19); Available at <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Myelog-Cisternog.pdf>. Accessed May 2, 2020.
- [10] Ray DE, Cavanagh JB, Nolan CC, Williams SCR. Neurotoxic effects of gadopentetate dimeglumine: behavioral disturbance and morphology after intracerebroventricular injection in rats. *AJNR Am J Neuroradiol* 1996;17:365–73.
- [11] Magnevist. (Gadopentetate dimeglumine) [product monograph]. Mississauga, Ontario, Canada: Bayer Inc; 2018.
- [12] Lin S-P, Brown JJ. MR contrast agents: physical and pharmacologic basics. *J Magn Reson Imaging* 2007;25(5):884–99.
- [13] Bellin M-F, Van Der Molen AJ. Extracellular gadolinium-based contrast media: an overview. *Eur J Radiol* 2008;66(2):160–7.