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Case Report

Persistence of Gadolinium in CSF: A Diagnostic Pitfall in Patients with End-stage Renal Disease

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Summary: Two dialysis-dependent patients with end-stage renal disease underwent brain and spine MR imaging a few days after having undergone gadolinium-enhanced imaging studies. Increased signal intensity in the subarachnoid space on T1-weighted and fluid-attenuated inversion recovery images was noted. Excretion of gadolinium into the CSF was proven in one case by mass spectrometry. Dialysis-dependent patients with end-stage renal disease and neurologic abnormalities often undergo contrast-enhanced MR imaging. Recognition that these patients may show increased signal intensity in the subarachnoid space because of gadolinium excretion into CSF may prevent diagnostic errors.

Patients with end-stage renal disease and neurologic abnormalities often undergo gadolinium-enhanced MR imaging. Recognition that these patients may show increased signal intensity in the subarachnoid space because of possible gadolinium excretion into CSF may prevent diagnostic errors.

This report presents two dialysis-dependent patients with end-stage renal disease with persistence of previously IV administered gadolinium in the subarachnoid space on MR imaging. The observation is presented with a brief discussion of gadolinium pharmacokinetics and the diagnostic pitfalls that may be encountered in this patient population.

Case Reports

Case 1

A 70-year-old woman with chronic renal failure secondary to focal segmental glomerulosclerosis had been on continuous ambulatory peritoneal dialysis for her renal failure. MR imaging of the brain was performed before and after IV gadolinium administration because of cognitive changes, fever, and concern for possible vasculitis. MR findings were unremarkable, apart from parenchymal volume loss and periventricular white matter changes consistent with chronic microvascular ischemia (Fig 1A–C). No abnormal contrast enhancement was present. One week later the patient underwent gadolinium-enhanced MR imaging of the abdomen for evaluation of peritonitis, and the examination was normal. Three days after gadolinium administration for the abdominal scan and 10 days after gadolinium administration for the initial brain scan, MR imaging of the brain was repeated for persistent mental status changes. This repeat MR imaging examination showed a striking interval change in the appearance of CSF in the subarachnoid space and, to a lesser extent, in the ventricular system. This was manifested as mild, diffusely increased signal intensity of the subarachnoid space on the precontrast sagittal and axial T1-weighted images (Fig 1D and E) and significantly increased signal intensity on the fluid-attenuated inversion recovery (FLAIR) images (Fig 1F). Increased signal intensity was also present in the aqueous and vitreous humor of both eyes on T1-weighted images. The possible etiologies considered were diffuse subarachnoid hemorrhage or elevated CSF cellular or protein content. CSF differential cell count was 3 white blood cells/μL and 1 erythrocyte/μL. CSF protein was mildly elevated at 85 mg/dL (normal range 15–45 mg/dL). High-resolution CSF protein electrophoresis revealed a mild increase in low-molecular-weight proteins in the CSF suggestive of a generalized alteration in the permeability of the blood-brain barrier.

The slightly elevated CSF protein was considered unlikely to cause the observed intracranial MR imaging findings and did not explain the ocular findings. A third possibility considered was the presence of gadolinium in the CSF, which could be accounted for by the inability of peritoneal dialysis to clear the contrast agent (administered 10 and 3 days earlier for the prior cranial and abdominal examinations) from the extracellular compartment, resulting in its increased bioavailability and subsequent mixing with or excretion into the CSF. To evaluate this possibility, a portion of the CSF sample drawn for laboratory evaluation was sent for mass spectrometric analysis (Mayo Medical Laboratories, Rochester, MN) for gadolinium. The CSF sample demonstrated extremely high concentrations (16250 ng/mL) of gadolinium, confirming its accumulation in or excretion into the subarachnoid space.

Case 2

The second patient was a 74-year-old woman with end-stage renal disease on hemodialysis (three times per week, 4 hours per session). She presented with bilateral hip and back pain accompanied by proximal muscle weakness. She was also found to have staphylococcus bacteremia. A contrast-enhanced MR imaging study of the hips was followed 2 days later by an MR imaging study of the lumbar spine. The patient had had 8 hours of hemodialysis since gadolinium injection for the hip MR imaging.

On the lumbar MR scan, there was diffuse increased signal intensity in the subarachnoid space on sagittal and axial precontrast T1-weighted images (Fig 2A and B). The study also demonstrated findings consistent with a ventral extradural abscess compressing the thecal sac between the second and fourth lumbar vertebral body levels. Gadolinium accumulation in or excretion into the CSF was considered the cause of T1 shortening on the precontrast images, given the patient's history of renal failure and the potential for incomplete clearance of the gadolinium (administered 2 days earlier for the hip MR scan) during hemodialysis. Her extradural abscess was surgi-

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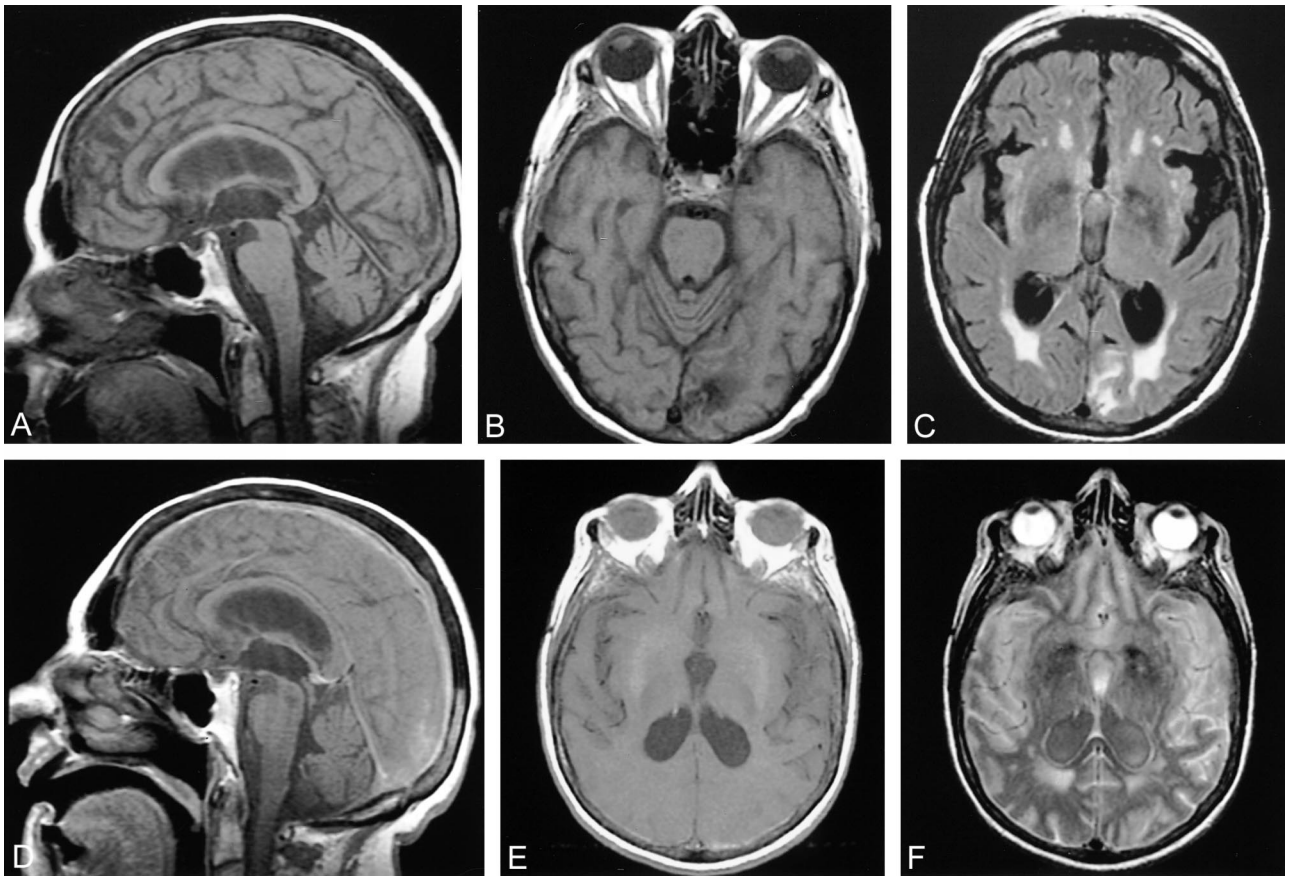

FIG 1. Sagittal (*A*) 500/8/1 (TR/TE/excitation) and axial (*B*) 566/12/1 precontrast T1-weighted and axial FLAIR (*C*) 10002/97.5/1 images of the brain demonstrate normal signal intensity of the CSF with normal contrast enhancement between the CSF and adjacent brain.

Sagittal (*D*) 500/8/1 and axial (*E*) 566/12/1 precontrast T1-weighted images 10 days later, demonstrate increased signal intensity within the subarachnoid space, manifested by an isointense appearance of the sulci as compared with the adjacent brain. Additionally, there is increased signal intensity within the ocular globes on the axial image. The axial FLAIR (*F*) 10002/97.5/1 image demonstrates diffuse significant increased signal intensity within the subarachnoid space and the ventricles. *A–F* were filmed at the same values for window and level, and were performed on the same scanner.

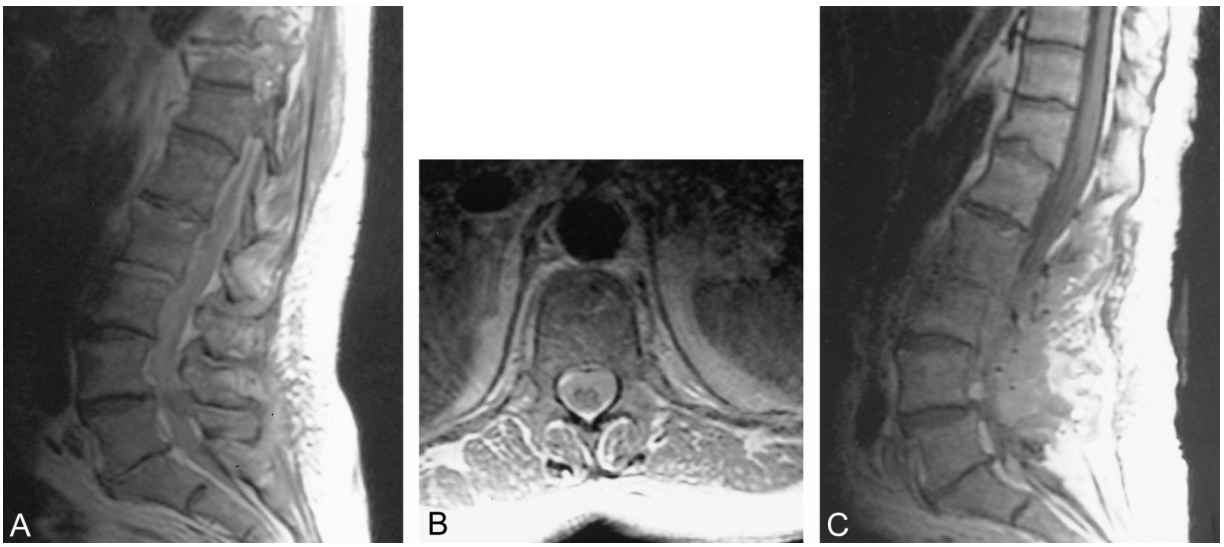

FIG 2. Sagittal (*A*) 516/12/2 and axial (*B*) 686/11.6/2 precontrast T1-weighted images of the spine demonstrate diffuse increased signal intensity within the subarachnoid space. Sagittal precontrast T1-weighted (*C*) 550/12/2 image of the lumbar spine performed 2 weeks later shows resolution of the previously seen increased signal intensity and a normal signal within the CSF. *A–C* were filmed at the same values for window and level, and were performed on the same scanner.

cally drained. An MR imaging study of the lumbar spine was repeated 2 weeks later, which showed resolution of the increased signal intensity in the subarachnoid space and the recent surgical change (Fig 2C).

Discussion

The pharmacokinetics of different gadolinium chelates have been studied in healthy patients and in those with varying degrees of renal impairment. After IV injection, the steady-state volume of distribution indicates predominantly extracellular distribution (1). The main pathway of elimination is glomerular filtration (1). The renal excretion rate indicates dose-proportionate first-order kinetics (1). The mean elimination half-life is 1.3 hours (2) to 1.5 hours (1, 3) in healthy subjects. In patients with renal failure, the predominant extracellular distribution of gadolinium at steady state does not change according to the degree of renal impairment (3). The mean elimination half-life has been shown to increase in relation to the degree of renal compromise (2–4). In patients with severe renal insufficiency, the half-life increased to 34.3 ± 22.9 hours (gadodiamide 0.1 mmol/kg) compared with healthy volunteers (1.3 ± 0.25 hours) in one study (2) and 7.4 ± 2.6 hours (gadobutrol 0.1 mmol/kg) and 17.9 ± 6.2 hours (0.1 mmol/kg) in patients with mild and moderate renal impairment, respectively, in another study (3). Elimination by means of glomerular filtration, however, remains the major route of excretion even in patients with severe renal failure (3, 5). Furthermore, after an IV injection, gadolinium is not metabolized in the body (1) and its plasma protein binding is negligible (3, 5). It has been shown that in patients undergoing hemodialysis, more than 12.2 to 14.7 hours of dialysis would be necessary to remove 97% of the injected dose of gadolinium chelate (6). In vitro studies showed that 11.1 hours of hemodialysis would be necessary to remove 97% of the injected dose (7). In another study, an average of 65% of injected gadolinium chelate (gadodiamide) was eliminated during a hemodialysis session, whereas after 22 days of continuous ambulatory peritoneal dialysis, 69% of the total amount of gadodiamide was excreted, indicating a considerably low peritoneal clearance (2).

In this report, the two patients' renal functions were maintained by peritoneal dialysis (case 1) and hemodialysis (case 2). Both patients had an MR imaging examination performed a few days after gadolinium administration for another study. Both patients demonstrated precontrast T1 shortening in the subarachnoid space, the first patient intracranially and in the eyes, and the second in the spine. The first patient had a mildly elevated CSF protein of 85mg/dL, insufficiently high to explain the observed increased intensity of CSF at the imaging parameters used (8). Mass spectrometry documented gadolinium concentration of 16,250 ng/mL in CSF, explaining the observed increased signal intensity.

As in the report of iodinated contrast accumulation resulting in increased CT attenuation in the CSF after overdose for spinal angiography (9), and in the cases of increased CSF signal intensity following contrast-enhanced perfusion MR imaging in the setting of stroke (10), it remains unclear precisely where the gadolinium entered the CSF in the two patients of the current report. We can speculate that the prolonged elevated concentration of gadolinium in the plasma in the absence of normal renal function results in prolonged, increased availability of circulating gadolinium in plasma. The increased plasma concentration of gadolinium (relative to that occurring in patients with normal renal function) would then tend to equilibrate among all the body's extracellular fluid compartments to the degree and rate allowed by the body's system of permeable and semipermeable membranes. Particularly, the intact endothelium of brain capillaries has tight junctions that are selectively permeable but highly restrictive to passage of solutes, such as gadolinium. Choroid plexus of brain and ciliary body of eye share histologic features for production of specialized fluids and have fenestrated capillary endothelia (11), and these fenestrations could be a site for contrast medium entry. This could account for some of the observed intraocular T1 shortening effect after contrast medium administration. However, there is restricted passage of molecules such as gadolinium from the extracellular space of the choroid plexus into the ventricles owing to tight junctions in apical portions of cuboidal epithelium of the choroid plexus (12).

Other possible sites where gadolinium may move along an osmotic gradient in the setting of prolonged elevation of plasma concentration include the circumventricular organs. These sites (pineal body, neurohypophysis, area postrema, and others) in the brain normally lack tight junctions in the capillary endothelium and allow passage of a variety of substances between the circulating blood and brain tissue (12), including iodinated and gadolinium contrast agents. The relatively less restrictive exchange between the extracellular fluid of the brain and the CSF at the ependymal surfaces and the pia-glial membrane (11) might promote accumulation of gadolinium in the CSF. This concept of interaction and exchange of molecules between the CSF and extracellular fluid of the brain as a site of dialysis has been referred to previously (13).

Furthermore, the generalized disturbance of blood-brain barrier, which was sufficient to allow 85 mg/dL of protein to accumulate in the CSF of the first patient, may have contributed to the accumulation of gadolinium in the CSF (10).

The observation of relatively less T1 shortening effect in the ventricular CSF compared with that in the subarachnoid spaces may reflect the effect of peritoneal dialysis. In the normal situation, continuous effective renal glomerular filtration almost im-

mediately begins decreasing the plasma concentration of injected gadolinium, and thus peak levels are short-lived. Dialysis-dependent patients retain injected gadolinium in their extracellular fluid volume until the next dialysis session. Until dialysis, most of the injected gadolinium has the opportunity to equilibrate in the extracellular fluid compartment. At dialysis, a fractional removal of gadolinium occurs, thus incrementally reducing the plasma concentration. When the plasma from which gadolinium has been dialysed circulates through choroid plexus, the newly elaborated CSF with relatively lower gadolinium concentration is secreted into the ventricles. We speculate that since the overall direction of movement of CSF is from the ventricles toward the subarachnoid space, the dilution effect is more pronounced in the ventricles, nearest the site of secretion of CSF with incrementally lower gadolinium concentrations with each fractional reduction following dialysis.

Previous work has addressed the phenomenon of accumulation of iodinated contrast material in the subarachnoid space in the settings of overdose of iodinated contrast, hypertension, and disruption of the blood-brain barrier due to infarction or neoplasm (9, 14, 15, 16). The high attenuation resulting may be initially attributed to subarachnoid hemorrhage, and the clinical picture may be further confusing because significant accumulation of iodinated contrast in the subarachnoid space has been associated in several cases with acute neurologic symptoms (9, 14, 15, 16). The authors of these reports describe the diagnostic importance of CSF sampling for laboratory analysis and review of the CT attenuation values in the CSF, which typically far exceed the expected attenuation values for subarachnoid hemorrhage (9, 16). Follow-up CT typically shows that iodinated contrast material clears from the subarachnoid space more quickly than subarachnoid blood (16).

Similarly, T1 shortening effect from gadolinium in the subarachnoid space on FLAIR MR images has been reported (10, 17, 18). Lev and Schaefer (19) described findings similar to those herein, reporting three patients who had either renal failure or elevated creatinine (19). Their analysis did not describe specific confirmation of gadolinium as the cause for the observed increased signal intensity in the CSF, but they did present evidence excluding elevated cell counts, elevated protein, and gross hemorrhage as the cause for this finding (19).

We believe the accumulation of gadolinium in these two dialysis-dependent patients with end-stage renal disease is analogous to iodinated contrast overdose in that the normal renal glomerular filtration function is absent. For the purpose of this discussion, overdose can be interpreted in a broad sense as administration of the gadolinium at a rate far exceeding the body's rate of elimination of it. Absent renal function allows the gadolinium to accumulate in and equilibrate over a prolonged period with the extracellular fluid volume. It is unknown what contributions are made by blood-brain–barrier disturbances or other speculative mechanisms of accumulation. The normally observed slightly transient T1 shortening effect in CSF after IV administered gadolinium decreases rapidly approximately 2 hours after injection (15).

The two cases document an interesting appearance of the CSF in patients with end-stage renal disease who underwent previous contrast-enhanced imaging. The duration of gadolinium persistence depends on the means of its removal, ie, peritoneal dialysis or hemodialysis. In such patients, the presence of gadolinium should be considered in the differential diagnosis for increased signal intensity in the CSF.

Gadolinium accumulation in the subarachnoid space is potentially an under-recognized finding, and may cause some confusion in diagnosis, analogous to the situation of iodinated contrast agent accumulating in the CSF. There is generally some reluctance among radiologists to administer iodinated contrast agent to patients with end-stage renal disease. Gadolinium-enhanced MR imaging is increasingly performed as an alternative diagnostic approach in this situation since the agent is well tolerated and generally represents a substantially smaller volume of solute and osmotic load compared with a similarly effective dosage of iodinated contrast agent. Gadolinium accumulation in the subarachnoid space may be attributed to other causes of proton-relaxation enhancement such as subarachnoid hemorrhage or markedly elevated CSF protein or cellular content from inflammatory or neoplastic involvement of the meninges and subarachnoid space. Patients with end-stage renal disease suffer complications of electrolyte alterations, infections, and hemorrhage that may alter CNS function and levels of consciousness, sometimes requiring multiple imaging evaluations of the CNS. This T1 shortening effect in the subarachnoid space can result in an appearance mimicking other known causes of altered CNS function in this particular patient population. It is helpful for radiologists and clinicians to understand that enhanced proton relaxation may result from residual gadolinium accumulating in the CSF. This understanding may prevent diagnostic errors or needless additional diagnostic examinations in these patients who are at increased risk for CNS infections, electrolyte shifts, or hemorrhage by virtue of their disease and its chronic treatment.

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