



COMMENTARY

Gadolinium-Induced Nephrogenic Systemic Fibrosis in Patients with Kidney Disease

Nephrogenic systemic fibrosis is a debilitating disease of uncertain cause that develops in patients with advanced chronic kidney disease and end-stage renal disease.¹ It is characterized by fibrosis, predominantly of the skin, which often leads to severe physical limitations (Figures 1 and 2). Systemic involvement of the liver, heart, lungs, diaphragm, and skeletal muscle also has been reported with fatal consequences.¹ Since its initial description in 1997, more than 200 cases have been described in the nephrogenic systemic fibrosis registry.¹ Ninety percent of these patients are dialysis-dependent, although non-dialysis-dependent patients with advanced chronic kidney disease and patients with acute kidney injury have been described.¹⁻⁴

Exposure to gadolinium from magnetic resonance imaging in patients with chronic kidney disease has been linked to nephrogenic systemic fibrosis.¹⁻⁴ Thirty patients with end-stage renal disease who developed nephrogenic systemic fibrosis after gadolinium exposure have been reported.²⁻⁴ The Food and Drug Administration also recently linked nephrogenic systemic fibrosis to gadolinium and released 2 Public Health Advisories. The first advisory reported nephrogenic systemic fibrosis in 25 patients with end-stage renal disease after gadolinium exposure; an up-



Figure 1 Brawny skin thickening and peau d'orange changes in the arm of a patient with nephrogenic systemic fibrosis (image courtesy of Shawn Cowper, MD, Yale University, with permission).



Figure 2 Skin thickening and its effect to cause an extension contracture of the foot in a patient with nephrogenic systemic fibrosis (image courtesy of Shawn Cowper, MD, Yale University, with permission).

date increased this to 90 patients.⁵ Free gadolinium has been documented within the fibrotic tissues of patients with nephrogenic systemic fibrosis, further incriminating gadolinium as the pathogenic trigger.⁶

Higher doses of gadolinium seem to increase the risk of nephrogenic systemic fibrosis. Broome and colleagues⁴ note an odds ratio of developing nephrogenic systemic fibrosis of 12.1 when comparing 0.2 mmol/kg dose with 0.1 mmol/kg dose. Magnetic resonance angiography (~0.3 mmol/kg) therefore carries a higher risk for nephrogenic systemic fibrosis than a nonvascular study (0.1 mmol/kg).

Gadolinium is predominantly cleared by the kidneys, and the $T_{1/2}$ of gadolinium in chronic kidney disease stages 4 and 5 (estimated glomerular filtration rate < 30 mL/min) is significantly increased.⁷ Gadolinium is dialyzed; however, it requires 3 treatments to remove more than 95% of an administered dose.⁷ Thus, tissue exposure to gadolinium is enhanced with advanced chronic kidney disease, and more so with higher doses.

Free gadolinium (Gd^{3+}) is toxic to tissues and unsafe for human use. To prevent toxicity, Gd^{3+} is bound to a chelate, an organic molecule that forms a stable complex around the Gd^{3+} . Gadolinium preparations differ predominantly in the chelate used. The majority of cases of nephrogenic systemic fibrosis have followed exposure to gadodiamide (Omniscan,

GE Healthcare, Piscataway, NJ),²⁻⁴ although this specific chelate was the only one used for magnetic resonance studies by reporting centers. Gadodiamide is less stable than other chelates⁷ and is more likely to dissociate into free Gd^{3+} . Still, nephrogenic systemic fibrosis has been reported with other gadolinium chelates, and caution should be observed with all gadolinium formulations in advanced chronic kidney disease.⁵

Although this is the early descriptive stage of a new disease, enough evidence is available to make some recommendations regarding gadolinium use in patients with chronic kidney disease. Patients on dialysis are at highest risk and should avoid exposure to gadolinium when possible. The judicious use of low/iso-osmolar iodinated radiocontrast with standard prophylaxis may be a better choice because iodinated radiocontrast-induced nephropathy is generally reversible and nephrogenic systemic fibrosis is not. If patients with end-stage renal disease must receive gadolinium, we recommend using the lowest dose possible, avoiding gadodiamide and performing hemodialysis immediately after and the next day after the procedure. The recommendations for gadolinium use in patients with chronic kidney disease stages 4 and 5 who are not receiving dialysis are similar with the exception of dialysis postexposure, although that option should be considered.

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Note Added in Proof

Since submission of this article, a total of 70 cases of NSF have been reported in the literature that link gadolinium exposure to the development of nephrogenic systemic fibrosis. Of these, 48 had ESRD, 10 had acute kidney injury, and 9 and 4 had chronic kidney disease stage 5 and 4, respectively.