Nephrogenic Systemic Fibrosis Associated With Gadoversetamide Exposure: Treatment With Sodium Thiosulfate

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Nephrogenic systemic fibrosis (NSF) is a debilitating fibrosing disorder of patients with kidney disease that is associated with gadolinium-based contrast exposure. Most cases are linked to gadodiamide. Gadoversetamide, an agent with chelate characteristics similar to gadodiamide, has rarely been described to cause NSF. With the exception of normalization of kidney function, there are no consistently effective therapies for patients with NSF. We describe 3 cases of NSF in patients with end-stage renal disease after gadolinium-based contrast exposure. Two patients received gadoversetamide and the third received gadodiamide. All 3 patients were treated early in their disease course with intravenous sodium thiosulfate and responded with improved skin changes and joint mobility.
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INDEX WORDS: Nephrogenic systemic fibrosis; gadolinium; gadoversetamide; gadodiamide; sodium thiosulfate; kidney disease.

Nephrogenic systemic fibrosis (NSF) is a debilitating systemic fibrosing disorder linked to gadolinium-based contrast exposure. Most published cases of NSF occurred after exposure to gadodiamide,[1] a nonionic linear chelate contrast agent. Conversely, gadoversetamide, a similar chelate, has been reported in only 3 published cases of NSF.[2] Although one would expect similar risk, the rarity of reports with gadoversetamide may relate to its small market share.

Treatment of patients with NSF has been disappointing. Aside from recovery of kidney function or successful kidney transplantation in patients with NSF, only extracorporeal photopheresis has shown some promise. Intravenous (IV) sodium thiosulfate (STS), a therapy used to prevent toxicity of cisplatin,[3] treat patients with cyanide poisoning, and improve ischemic lesions caused by calcific uremic arteriolopathy, showed promise in patients with NSF both anecdotally and in a single case report.[4] Conversely, 4 patients with advanced NSF treated with STS garnered little clinical benefit.[5]

We describe 3 cases of NSF that developed in patients with end-stage renal disease (ESRD) after gadolinium-based contrast exposure. Two patients received gadoversetamide, and all 3 showed significant improvement in dermal changes and joint mobility after IV STS therapy.

CASE REPORTS

Case 1

A 22-year-old African American woman with ESRD on automated peritoneal dialysis therapy presented with progressively worsening pain, pruritus, and swelling of her hands and legs (Table 1).

The patient received a deceased-donor kidney transplant, but developed posttransplantation lymphoproliferative disease, which led to loss of her transplanted kidney. Brain magnetic resonance imaging with IV gadodiamide (0.1 mmol/kg) was performed to evaluate headache and chronic recurrent nausea and vomiting. Three days later, the second gadodiamide-based contrast magnetic-resonance imaging (0.1 mmol/kg) was performed of the abdomen to evaluate abdominal pain. A third gadodiamide-based study (0.1 mmol/kg) was obtained a day later.

During the next 6 weeks, she developed terrible extremity pain with pruritus and swelling. This progressed to skin tightening and extremity weakness with loss of joint mobility.

On examination, vital signs were within normal limits. No scleral plaques were present, and neck, lung, heart, and abdominal examination findings were within normal limits. Symmetric thickening and woody edema of the skin extending from both hands up to the elbows and both feet up to midthigh were noted. The skin was modestly erythematous and warm. The edema was nonpitting and "unpinchable." Movements were restricted in both hands and legs.

A clinical diagnosis of NSF was considered based on the skin changes and gadodiamide exposure. Skin biopsy findings were consistent with early NSF, with a few collagen bundles in the reticular dermis and subcutaneous septum noted on scanning microscopy (Fig 1). Increased numbers of

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Table 1. NSF Cases

Patient No.	Age (y)	Comorbid Diseases	Medications	Dialysis Modality	Time From Gd to NSF and STS Rx	STS Dose (3×/wk)	Time From STS to Improvement
1	22	SLE, hypertension, hypothyroid, lymphoma	Paracalcitol, trazodone, erythropoietin, methadone, cinacalcet, prednisone, ondansetron, lanthanum	Hemodialysis, automated peritoneal dialysis	6 wk	25 g (×5 doses) 12.5 g (×8 doses)	2 wk
2	64	Anemia, CAD, morbid obesity, sleep apnea, diabetes mellitus, neuropathy	Erythropoietin, allopurinol lanthanum, aspirin, clonazeoam, ezetimibe, cinacalcet, lansoprazole	Hemodialysis	2 mo	12.5 g (×96 doses)	2 mo
3	62	Diabetes mellitus, hypertension, CAD, sleep apnea, CUA	Aspirin, cinacalcet, fenofibrate, metoclopramide, sevelamer, valsartan, erythropoietin, pioglitazone	Hemodialysis	8 mo	25 g (×12 doses) 12.5 g (×48 doses)	2 mo

Abbreviations: CAD, coronary artery disease; CUA, calcific uremic arteriolopathy; Gd, gadolinium; Rx, prescription; SLE, systemic lupus erythematosus; STS, sodium thiosulfate.

diffusely distributed bland thin spindle cells were noted in the reticular dermis (Fig 2A) that stained positively for procollagen I (Fig 2B) and CD34 (Fig 2C).

After the diagnosis of NSF, physical therapy and pain control were initiated. Treatment with IV STS was initiated, and STS was administered thrice weekly over 30 minutes through a tunneled venous catheter. The patient received 25 g for the first 5 doses, which was decreased because of nausea to 12.5 g for 8 doses. After 2 weeks, softening of the thickened and indurated skin and increased joint mobility were noted. Over time, the patient described less pain, improved mobility, and skin softening with continued STS treatment. Approximately 2 months later, the patient developed severe septic shock. The upper and lower extremities had no edema and little evidence of skin induration or thickening. Unfortunately, the patient died.

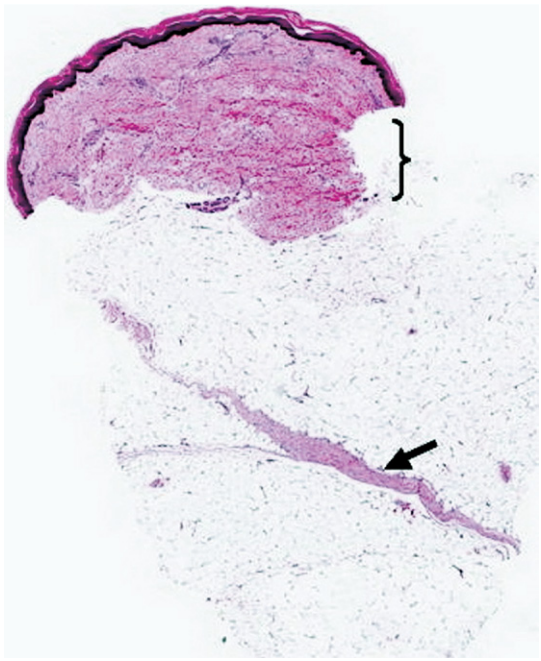

Figure 1. Scanning magnification image shows minimal thin collagen bundles in the slightly thickened dermis (bracket) and subcutaneous septum (arrow).

Case 2

A 64-year-old white man with ESRD on hemodialysis therapy presented with progressive swelling of both hands and feet with restriction of movements over 1 to 2 months (Table 1).

The patient underwent neck magnetic resonance imaging (gadoversetamide, 0.1 mmol/kg) 3 months prior for evaluation of parathyroid adenoma followed by magnetic resonance angiography (gadoversetamide, 0.3 mmol/kg) of his arteriovenous fistula 2 months prior.

On examination, vital signs were within normal limits. No scleral plaques were noted, and lung, heart, and abdominal examination findings were within normal limits. Symmetric thickening and woody edema of the skin extending from both hands to the elbows and both feet to the ankles were noted. The edema was nonpitting and unpinchable. Movements were restricted in both hands.

A clinical diagnosis of NSF was made, and skin biopsy confirmed early NSF with relatively few collagen bundles present.

The patient underwent physical therapy and IV STS (12.5 g thrice weekly over 15 minutes) infusions at the end of hemodialysis for 6 months. After 2 months, improvement in skin texture with a reduction in woody induration and increased mobility of the hands and wrists were noted.