

# Nephrogenic Systemic Fibrosis: A Population Study Examining the Relationship of Disease Development to Gadolinium Exposure

Aneet Deo,\* Mitchell Fogel,<sup>†‡</sup> and Shawn E. Cowper<sup>§</sup>

\*Department of Medicine and <sup>†</sup>Division of Nephrology, St. Vincent's Medical Center, Bridgeport, Connecticut;

<sup>‡</sup>Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York; and

<sup>§</sup>Departments of Dermatology and Pathology, Yale University School of Medicine, New Haven, Connecticut

Nephrogenic systemic fibrosis (NSF) is a devastating complication of severe renal failure. Recent reports suggest that exposure to gadolinium-containing contrast agents (GCCA) is associated with the occurrence of NSF. The population of patients with ESRD in and around Bridgeport, CT, was studied during an 18-mo period. The incidence of NSF was 4.3 cases per 1000 patient-years. Each radiologic study using gadolinium presented a 2.4% risk for NSF. The association between gadolinium exposure and NSF was highly significant ( $P \leq 0.001$ ). It is concluded that GCCA exposure is a major risk factor for NSF in the ESRD population. Because of the significant morbidity and mortality with NSF, it is believed that gadolinium exposure should be avoided in patients with ESRD. In the event that exposure cannot be avoided, careful consideration of the potential consequences, including a thorough discussion of the risks and benefits of GCCA, is advised.

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**N**ephrogenic systemic fibrosis (NSF) is a systemic disorder that is characterized by thickening and tightening of the skin and subcutaneous tissues (1). First observed in 1997, NSF was originally known as nephrogenic fibrosing dermopathy because of its classic presentation of symmetric, brawny, or erythematous indurated cutaneous plaques that develop in the setting of renal insufficiency (2,3). Recognition that this syndrome can include fibrosis of skeletal muscle, lung, liver, testes, or myocardium with possible fatal outcomes led to the adoption of the more recent nomenclature: Nephrogenic systemic fibrosis (4,5).

The cause of NSF remains speculative. Hypercoagulation syndromes, anti-phospholipid antibodies, deep vein thrombosis, metabolic acidosis, erythropoietin administration, and surgical or vascular interventions all have been implicated as possible contributing factors (6–9). Several recent reports described the development of NSF after gadolinium exposure (9–11). To follow up on these reports, we reviewed the use of gadolinium in our long-term dialysis population during an 18-mo period and analyzed its relationship to the development of NSF.

## Materials and Methods

We retrospectively analyzed data from a population of patients who had ESRD and were living in the nine urban and suburban communi-

ties that surround Bridgeport, CT. The study population consisted of patients who had ESRD and were treated at one of three hemodialysis facilities or one peritoneal dialysis facility on July 1, 2006. These four programs were the only dialysis facilities in this geographic area, thus providing a population based study.

Within this population, three cases of NSF were diagnosed in the 18-mo period that ended on July 1, 2006. Patients were identified on clinical grounds with confirmatory skin biopsies. The relationship between gadolinium exposure and NSF was documented, and details of the cases were recorded. The remaining patients who had ESRD and did not develop NSF served as the control group.

We manually reviewed data from all of the radiology practices in this region to identify how many of patients with ESRD were exposed to gadolinium during the 18-mo period from January 1, 2005, through June 30, 2006. Data on both NSF case patients and control subjects were recorded. Because some individuals had more than one gadolinium exposure, the number and the nature of gadolinium-based studies were recorded. There were no exclusion criteria.

Incidences were calculated using standard methods. Because of the small sample size, the statistical analysis was performed using Fisher exact test, with  $P \leq 0.05$  required for significance. A Web-based statistical tool was used to perform the statistical calculation (12).

## Results

Three cases of NSF were diagnosed in this population with ESRD during the 18-mo period from January 1, 2005, through June 30, 2006. As illustrated in Table 1, all three cases occurred within 2 mo of gadolinium exposure. Two of the three cases had fatal courses. One patient died as a direct consequence of NSF. Progressive skin contractures with an associated myopathy and severely impaired quality of life led to a decision to stop dialysis. In the other fatal case, NSF-related pulmonary fibrosis was complicated by recurrent respiratory infections

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**Address correspondence to:** Dr. Shawn E. Cowper, Department of Dermatology, Yale University School of Medicine, 15 York Street, LMP 5031, New Haven, CT 06520. Phone: 203-785-4094; Fax: 203-785-6869; E-mail: [shawn.cowper@yale.edu](mailto:shawn.cowper@yale.edu)

Table 1. NSF cases<sup>a</sup>

Patient (Age, Race, Gender)	Study Performed (Contrast, Dosage, Date of Exposure)	Onset of Symptoms	Treatment	Course
1. 62, black, male	MRI left foot (MV, 20 ml, 3/17/05)	4/25/2005	None	Progressive, fatal
2. 70, white, male	Fistulogram ×3 (OS, 50 ml 12/2/05; 30 ml, 12/6/05; 30 ml, 1/2/06)	2/8/2006	Steroids, physical therapy	Progressive, fatal
3. 49, white, female	MRI brain (OS, 125 ml, 1/16/06)	3/23/2006	None	Stable

<sup>a</sup>MV, Magnevist (Gadopentetate Dimeglumine, Berlex Laboratories, Montville, NJ); NSF, nephrogenic systemic fibrosis; OS, Omniscan (Gadodiamide, Amersham, Buckinghamshire, UK).

and ventilatory failure. Only one patient had been clinically stable, and none had a spontaneous improvement.

The association of gadolinium exposure with the development of NSF is shown in Table 2. A total of 87 patients with ESRD had 123 radiologic studies with gadolinium during the study period. All three of the NSF cases occurred in patients after gadolinium exposure, and no patient who had ESRD and was unexposed to gadolinium developed NSF. There was a highly significant association ( $P = 0.006$ ) between patient exposure to gadolinium and the subsequent development of NSF in this ESRD population. Multiple gadolinium studies were occasionally performed on the same patient. For this reason, the association between gadolinium studies and the development of NSF was also examined. The association of gadolinium studies, as was the per-patient analysis, was also highly significant ( $P \leq 0.001$ ).

The ESRD population of 467 patients in this geographic area was relatively stable during the study period. This allows the calculation of a crude NSF incidence rate, shown in Table 3, of 0.0043 cases per patient per year, or 4.3 cases per 1000 patient-years (4.3 cases per 1000 patients, annually). The 95% confidence interval for the incidence ranged between 1.3 and 7.3 cases per 1000 patient-years. The absolute risk for development of NSF was 3.4% when a member of the ESRD population received gadolinium. Each radiologic study that included gadolinium presented a 2.4% risk for development of NSF. Because no cases of NSF occurred without gadolinium exposure, a relative risk could not be calculated.

A review of both inpatient and outpatient radiology studies during this time interval found that 87 patients with ESRD received gadolinium in a total of 123 studies, or 0.39 studies per patient per year. The most commonly performed study was magnetic resonance imaging/magnetic resonance angiography of the abdomen and pelvis (27.6%) followed by magnetic res-

onance imaging of the brain (22%). A majority (62 [71%] of 87) of the exposed ESRD population had only one gadolinium study. A minority of the exposed population (25 [29%] of 87) had two or three gadolinium studies during the study period. As shown in Table 4, we were not able to establish that multiply exposed patients had a higher risk for developing NSF than patients who had received a single exposure.

## Discussion

The most recent literature regarding NSF describes onset shortly after gadolinium exposure (9,10). Grobner (9) reported of nine hemodialysis patients in Austria who were exposed to gadolinium, five developed NSF. The population of patients with ESRD was not described. Marckmann *et al.* (10) reported on 13 cases of NSF from Denmark, all of whom received gadolinium before the onset of symptoms. The Food and Drug Administration recently identified the risk for this potential association between gadolinium and NSF and cautioned against the use of this agent in those with renal insufficiency (13). We sought to expand on these findings and performed a population-based study in which incidence of NSF, risk after gadolinium exposure, and statistical association between gadolinium administration and NSF could be analyzed.

In our study, all three cases of NSF developed after the administration of gadolinium. It is interesting that our initial experience with NSF occurred 5 yr before the current series (and is not included in this study). In retrospect, that patient had received gadolinium 3 mo before the onset of symptoms. In our current study, we found no cases of NSF without previous gadolinium exposure. Our data establish a strong statistical association between NSF onset and previous gadolinium use ( $P < 0.001$ ), similar to the findings of Marckmann *et al.* (10).

We believe that our report is the first to confirm the association between gadolinium and NSF in an American dialysis

Table 2. Association between NSF and exposure to gadolinium-based contrast<sup>a</sup>

Exposure	Gadolinium Exposures	No Gadolinium Exposure	Total
NSF cases	3 patients (5 studies)	0	3
No NSF	84 patients (118 studies)	380	464
Total	87 patients (123 studies)	380	467

<sup>a</sup>Using per-patient data, Fisher exact test  $P = 0.006$ ; using per-study data, Fisher exact test  $P \leq 0.001$ .

Table 3. Incidence of NSF and risk with gadolinium

Parameter	Rate
Incidence of NSF	3 of 467 over 1.5 yr (4.3 per 1000 patient-years)
Risk for NSF per patient	3 of 87 (3.4%)
Risk for NSF per gadolinium study	3 of 123 (2.4%)

Table 4. Association between single and multiple exposures to gadolinium and the development of NSF<sup>a</sup>

Exposure	Patients with Single Gadolinium Exposure	Patients with Multiple Gadolinium Exposures	Total
NSF cases	2	1	3
No NSF	60	24	84
Total	62	25	87

<sup>a</sup>Degrees of freedom = 1;  $\chi^2 = 0.032$ ;  $P = \text{NS}$ .

population. Although small in size, our population-based study documents an incidence of NSF of 4.3 cases per 1000 patient-years. The risk for NSF with gadolinium was 3.4% per patient, or 2.4% per gadolinium exposure. This is much lower than the 55% incidence rate in the study by Grobner (9). We cannot explain the dramatic difference in the incidence of NSF after gadolinium exposure compared with the Austrian report. Our hemodialysis population received dialysis using Polyflux dialyzers. The dialysis membrane that was used in the report by Grobner was not described. We cannot exclude the possibility that our hemodialysis treatments were more effective in removing gadolinium, leading to a lower risk for NSF after exposure. We believe that our data are representative of the American experience.

We did not collect data on gadolinium dosage in unaffected patients. For this reason, we cannot comment on whether the dosage of gadolinium increased the risk for NSF. That multiple gadolinium studies did not seem to increase the risk for NSF compared with those who received only a single study suggests against a cumulative dosage effect, however.

Among the three cases described herein, two different formulations of gadolinium-containing contrast agents, produced by two different companies, are represented. Gadodiamide (Amersham, Buckinghamshire, UK), which is the same agent associated with the European reports (9,10), was associated with two cases in our series, whereas Gadopentetate Dimeglumine (Berlex Laboratories, Montville, NJ) was associated with one case. These agents represent the two most commonly used gadolinium-based contrast agents in the United States (with a total of five approved by the Food and Drug Administration).

Each of our three cases occurred in hemodialysis patients and none in the peritoneal dialysis population. The small numbers made it difficult to do a separate analysis according to dialysis modality. If the study were limited to hemodialysis patients alone, then the statistical association would likely be more significant.

The risks of contrast agents are widely known to both nephrologists and radiologists. The incidence of contrast nephropathy

from iodinated contrast has been reported to vary between 1.6 and 11.8%, depending on the definition of acute renal failure (ARF) and the presence or absence of diabetes or baseline renal insufficiency (14,15). Gadolinium can rarely be associated with ARF (16,17). One recently reported case of gadolinium-induced ARF showed biopsy findings that were consistent with acute tubular necrosis (18). We believe that NSF should be recognized as another potential complication of gadolinium exposure. Two recent reports that gadolinium can be detected in the skin of patients with NSF (11,19) serve to support this association.

NSF is at least as serious as contrast media-induced ARF. The risk for development of NSF after a gadolinium study in a patient with ESRD, 2.4%, seems to be within the range of reported risks for ARF from iodinated contrast in a hospitalized patient. Unlike contrast nephropathy, for which a return to normal renal function occurs in most patients, NSF commonly has a continuous or progressive course. Spontaneous resolution of NSF has not been described in any of the reported series (1,4,6,7). Contrast nephropathy from iodinated dye can be associated with an in-hospital mortality of up to 14.9% (20). Although our mortality from NSF, 67%, was higher than that in other reported series, it highlights that NSF can be a life-threatening complication.

The major limitations of our study are its small size and its retrospective nature. The study population was not constant because of continuous influx and efflux of patients; a prospective study might obtain a different incidence. Because of growing awareness of the association between gadolinium and NSF, such a prospective study is unlikely to be performed. Our total population remained stable during the 18-mo study period; therefore, we believe that our incidence data are accurate. There is a possibility that cases of NSF could have been missed, thereby underestimating the incidence. Because of our previous experience with this syndrome, we do not believe that this is likely.

The greatest strength of this study is that it is population based. Our study population is a single nephrology practice that is the sole provider of dialysis services in a defined geo-

graphic area. We reviewed dialysis records as well as information from both inpatient and outpatient radiology practices to obtain our data. We believe that our ability to show a statistically significant association despite our small sample size increases the likelihood that others will confirm our findings.

The finding of an NSF incidence of 4.3 cases per 1000 patient-years, a 2.4% risk for NSF for each gadolinium exposure, the strong statistical association between NSF and gadolinium, and the unrelenting clinical manifestations of NSF should serve as a warning to health care providers. On the basis of this information, we believe that gadolinium exposure should be avoided in patients with ESRD whenever possible. In the event that exposure cannot be avoided, careful consideration of the potential consequences, including a thorough discussion of the risks and benefits of any anticipated radiologic study that uses gadolinium-containing contrast, is advised.

Cases of nephrogenic systemic fibrosis can be submitted to the International NSF Registry by following instructions on the Registry website at <http://www.icnfd.org>.

## Disclosures

None.

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See the related editorial, “Nephrogenic Systemic Fibrosis, Kidney Disease, and Gadolinium: Is There a Link?” on pages 200–202.