

# Nephrogenic Systemic Fibrosis, Kidney Disease, and Gadolinium: Is There a Link?

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**N**ephrogenic systemic fibrosis (NSF), formerly known as nephrogenic fibrosing dermopathy (NFD), is now a major concern for nephrologists. This entity was first described in 1997 in renal transplant recipients with poor graft function (1). More than 215 cases of NSF have subsequently been described in the NFD/NSF registry, with increasing numbers of cases being reported (2). NSF is a fibrosing disorder that involves predominantly the skin but also affects systemic organs such as the liver, heart, lungs, diaphragm, and skeletal muscle (3). It is associated with severe physical disability and death when multisystem disease supervenes (3). The cause of NSF is unknown; however, underlying kidney dysfunction is present in all cases. Approximately 90% of the patients described in the registry have ESRD and are on either hemodialysis or peritoneal dialysis (2). The rest have chronic kidney disease (CKD) or developed NSF in the setting of acute kidney injury (AKI). Thus, underlying kidney disease is a requisite for NSF to occur. Because not all patients with kidney disease develop NSF, one must hypothesize that a trigger is required to set the “fibrosing process” into motion.

What do we know about the histology of tissue fibrosis in NSF? Dermal spindle cells, the predominant cell type found in NSF biopsies, have an immunologic profile (CD34/procollagen I) that is identical to blood-borne cells, circulating fibrocytes (cF), which participate in normal wound healing (4). In the setting of tissue/endothelial injury, they enter tissues and engage in wound healing and scar formation. In NSF, however, this process differs from normal wound healing in that cF engage in this activity in the absence of a clinically evident wound. The disturbed environment of kidney disease may supply abnormal signals, which result in cF entry into normal tissues and induction of fibrosis (4).

A logical first step to determine the cause of NSF (and why cF inappropriately enter normal tissues) is to examine the underlying characteristics of the host. Uniformly, every patient who has developed NSF had abnormal kidney function. Parenthetically, restoration of renal function in renal transplant recipients and recovery from AKI are noted to regress or stabilize the

fibrotic process. Why does underlying kidney disease promote or facilitate the development of NSF? The dialysis procedure itself initially was a major suspect but no longer because NSF develops in patients who have never undergone dialysis (10%) and is absent in the majority of patients who are on long-term maintenance dialysis. Endothelial injury, common in patients with ESRD and CKD, may be one of the critical risk factors by permitting platelets to interact and attach to injured/exposed endothelium (as occurs in normal wound healing). Along this line of reasoning, vascular trauma and thrombotic events occur commonly in patients with ESRD/CKD. Vascular surgical procedures, central catheter placement, deep venous thrombosis, right atrial clots from indwelling catheters, and thrombosed vascular accesses are frequently present before the development of NSF (5). Also, a variety of previously unsuspected hypercoagulable states are uncovered after diagnosis of NSF. One may speculate that the state of “vascular/endothelial dysfunction” that is present in patients with kidney disease (6) primes them for a second event, or “trigger,” that sets the fibrosing process into motion.

The trigger for NSF is unknown, but the magnetic resonance imaging (MRI) contrast agent gadolinium ( $Gd^{3+}$ ) has become the leading suspect. In this issue of the *Clinical Journal of American Society of Nephrology*, two articles describe  $Gd^{3+}$  exposure before the development of NSF in patients who had ESRD and were on dialysis (7,8). A small population study of patients with ESRD that was conducted during an 18-mo period by Deo *et al.* (7) notes an NSF incidence of 4.3 cases per 1000 patient-years and a 2.4% risk for each  $Gd^{3+}$  exposure. Yerram *et al.* (8) describe NSF in a patient who had ESRD and was exposed to multiple doses of  $Gd^{3+}$ , suggesting dosage-related toxicity or requirement of another co-factor (in addition to  $Gd^{3+}$ ) to trigger NSF. Grobner (9) initially observed NSF in five patients with ESRD after  $Gd^{3+}$  contrast exposure, a finding that subsequently was confirmed in another 13 patients with ESRD (10). The NFD/NSF registry data reveal that all patients with available data were exposed to  $Gd^{3+}$  before the development of NSF (3). In a personal communication, Dr. Henrik Thomsen (Copenhagen University, Copenhagen, Denmark; December 12, 2006) noted that  $Gd^{3+}$ -associated NSF has now been reported in most European countries, including Denmark, United Kingdom, Austria, Belgium, The Netherlands, Norway, Sweden, and Switzerland. Two recently published studies document  $Gd^{3+}$  within tissues of five patients with NSF using scanning electron

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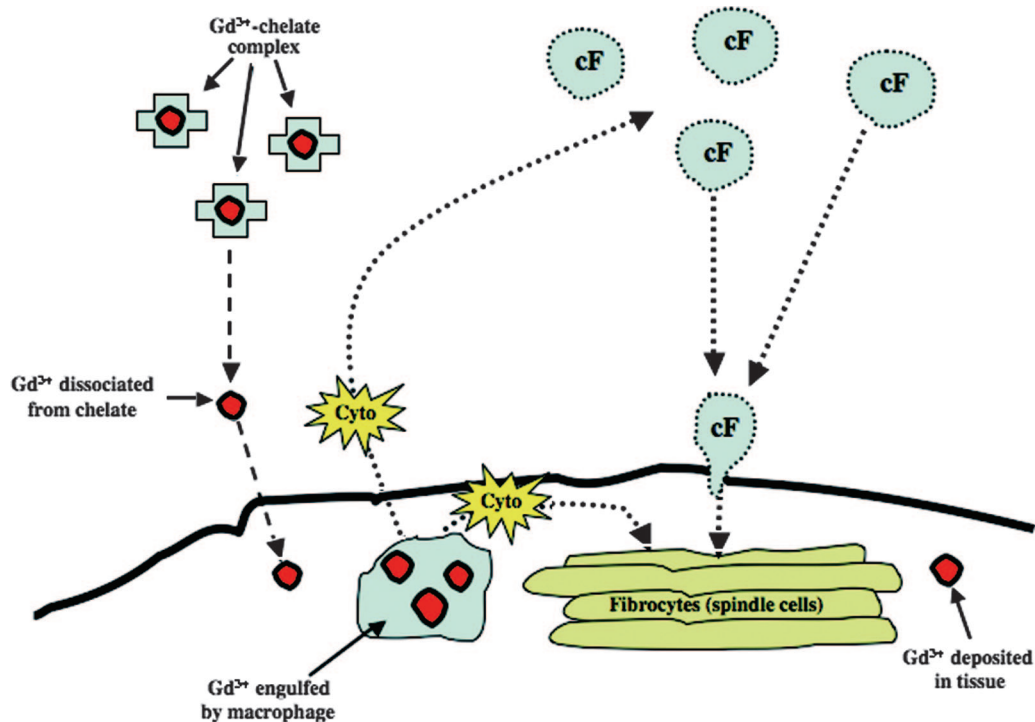
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microscopy and energy dispersive x-ray spectroscopy, further evidence of  $Gd^{3+}$ 's potential role as a trigger (11,12).

$Gd^{3+}$  may act as a trigger for NSF in patients with kidney disease on the basis of its reduced clearance and possibly its chelate-binding characteristics.  $Gd^{3+}$  contrast is eliminated almost entirely (97%) by the kidneys (13). Reduced renal function significantly increases the half-life of  $Gd^{3+}$  from 1.96 h in healthy individuals to 5.61 and 9.18 h in stages 4 and 5 CKD, respectively (13). In patients who have ESRD and are on hemodialysis,  $Gd^{3+}$  is substantially removed (>95%) only after three hemodialysis treatments (14) and is poorly removed by peritoneal dialysis (15). Therefore, tissue exposure to  $Gd^{3+}$  is prolonged. Free  $Gd^{3+}$  is toxic to tissues and unsafe for human use. For prevention of toxicity,  $Gd^{3+}$  is sequestered by binding it to a chelate, which is an organic molecule that forms a stable complex around the  $Gd^{3+}$ .  $Gd^{3+}$  is classified into four major categories on the basis of chelate biochemical structure (macrocytic *versus* linear) and chelate charge (ionic *versus* nonionic). Macrocytic chelates bind  $Gd^{3+}$  more tightly than linear chelates, are more stable both *in vitro* and *in vivo*, and have lower dissociation rates (16). Gadodiamide, the agent that most commonly is associated with NSF, is a nonionic contrast agent that uses a linear chelate. Gadopentetate, described in one of the NSF cases in this issue (7), also uses a linear chelate. Therefore, it is possible that the linear chelate characteristic makes certain  $Gd^{3+}$  formulations less stable and more likely to dissociate. In

fact, as compared with gadoteridol, a macrocytic chelate, gadodiamide leaves two to four times more  $Gd^{3+}$  in bone tissue of patients with normal kidney function (17). The relative instability of gadodiamide may underlie its excess association with NSF. This remains to be proven, and until there is adequate evidence, all  $Gd^{3+}$  formulations should be viewed with concern. Taken together, prolonged tissue exposure occurs in patients with CKD/ESRD (reduced renal clearance), which may allow free  $Gd^{3+}$  (released from its chelate) to extravasate from abnormal vessels (*e.g.*, from vascular trauma, endothelial dysfunction, chronic edema) and deposit in tissues. Once in tissues,  $Gd^{3+}$ -containing macrophages produce profibrotic cytokines that act locally and attract cF, which promote the fibrotic response (Figure 1).

Although cause and effect have not been proven with  $Gd^{3+}$  exposure and development of NSF, there is compelling associative evidence to recommend limiting  $Gd^{3+}$  exposure to patients with kidney disease. Dialysis patients are clearly at risk and should avoid  $Gd^{3+}$  at all costs. However, are those with an estimated GFR <30 ml/min (CKD stages 4/5) also at risk? Because 10% of patients who developed NSF had either AKI or CKD but never underwent dialysis, risk seems to extend beyond the dialyzed ESRD population. Therefore, it may be prudent to include those who are approaching the need for long-term maintenance dialysis, those who are awaiting preemptive renal transplantation, and those with advanced chronic allo-



**Figure 1.** Speculative mechanism by which gadolinium ( $Gd^{3+}$ ) might trigger nephrogenic systemic fibrosis. In the setting of kidney disease, impaired renal excretion of  $Gd^{3+}$  prolongs the half-life and enhances the chance for dissociation of  $Gd^{3+}$  from its chelate, allowing increased tissue exposure. Vascular trauma and endothelial dysfunction allow free  $Gd^{3+}$  to enter tissues more easily, where macrophages phagocytose the metal and produce local profibrotic cytokines as well as signals that attract circulating fibrocytes to the tissues. Once in tissues, circulating fibrocytes induce a fibrosing process that is indistinguishable from normal scar formation. cyto, cytokines; cF, circulating fibrocyte.

graft nephropathy as part of the risk group. If MRI with Gd<sup>3+</sup> is to be avoided, then iodinated radiocontrast-based imaging may be the only alternative when other noninvasive studies are insufficient. One is left to ponder whether the potential risk for NSF (and its devastating consequences) from Gd<sup>3+</sup> is more dangerous than radiocontrast-induced nephropathy (and its mortality risk) in patients with advanced kidney disease. Currently, there is no clear-cut answer, but because radiocontrast-induced nephropathy is generally reversible and NSF is not, exposure to radiocontrast is probably preferable.

For the time being, it is best to avoid administration of Gd<sup>3+</sup> to patients with AKI and stage 4/5 CKD (including transplant patients) and those who are on dialysis. Judicious use of iodinated radiocontrast (small volumes, low/iso-osmolar) with standard prophylaxis (intravenous fluids, N-acetylcysteine) may be a better choice. If an MRI study with contrast is absolutely required, then a nongadodiamide contrast using the lowest possible dosage is preferable. In hemodialysis patients, it would also seem prudent to perform dialysis after Gd<sup>3+</sup> exposure and then again the day after exposure to enhance Gd<sup>3+</sup> elimination. Because peritoneal dialysis clears Gd<sup>3+</sup> inefficiently, temporary hemodialysis after exposure may be a consideration. Also, other potential co-factors (*e.g.*, acidosis, erythropoietin, intravenous iron, hyperphosphatemia) need to be identified, because Gd<sup>3+</sup> exposure alone is insufficient. These recommendations are not evidence based but rather are derived purely from associative data on the NSF-Gd<sup>3+</sup> link. In patients in whom NSF has developed, intravenous sodium thiosulfate, as successfully used by Yerram *et al.* (7), may provide some benefit (in addition to aggressive physical therapy). Sodium thiosulfate may act by chelating Gd<sup>3+</sup> and improving endothelial function through its antioxidant effects. Because deposition of Gd<sup>3+</sup> in tissues and “endothelial dysfunction” may be critical aspects of NSF, they are logical targets of therapy.

## Disclosures

None.

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See the related articles “A Population Study Examining the Relationship of Disease Development to Gadolinium Exposure,” on pages ●●●-●●●, and “Nephrogenic Systemic Fibrosis: A Mysterious Disease in Patients with Renal Failure—Role of Gadolinium-Based Contrast Media in Causation and the Beneficial Effect of Intravenous Sodium Thiosulfate,” on pages ●●●-●●●.

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

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

| Patient<br>(Age, Race, Gender) | Study Performed<br>(Contrast, Dosage,<br>Date of Exposure)           | Onset of<br>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;<br>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<br>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.icnldr.org>.

## Disclosures

None.

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# Nephrogenic Systemic Fibrosis: A Mysterious Disease in Patients with Renal Failure—Role of Gadolinium-Based Contrast Media in Causation and the Beneficial Effect of Intravenous Sodium Thiosulfate

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Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NSF) is an emerging scleromyxedema-like cutaneous disorder of unknown cause that is seen in patients with renal failure, and the number of reported cases has grown significantly since its first recognition. Recent case reports associated the use of gadolinium ( $Gd^{3+}$ )-based contrast agents with the development of NSF. Herein is reported an additional patient who had NSF and had multiple previous exposures to  $Gd^{3+}$ -based magnetic resonance imaging studies and had marked improvement in pain and skin changes after a trial of intravenous sodium thiosulfate. Discussed are the possible association of  $Gd^{3+}$ -based contrast media with the development of NSF and potential for the use of sodium thiosulfate in the treatment of NSF.

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**N**ephrogenic fibrosing dermopathy (NFD) is an emerging scleromyxedema-like disease that is seen in patients with renal failure (1). This condition is characterized by thickening, induration, and hardening of the skin and requires skin biopsy for confirmation. Furthermore, this condition extends beyond the dermis, involving multiple organs and tissues, prompting it to be renamed nephrogenic systemic fibrosis (NSF) (2,3). The exact cause/trigger and treatment for this condition are still obscure. Recently, an association with exposure to gadodiamide (gadolinium [ $Gd^{3+}$ ]-diethylenetriaminepentaacetic acid) and the development of NSF has been described (4,5) and has prompted the US Food and Drug Administration (FDA) to issue a public health advisory regarding the use of  $Gd^{3+}$ -containing magnetic resonance imaging (MRI) contrast agents in patients with advanced renal failure (6). Recent findings of  $Gd^{3+}$  in the skin of patients with NSF has further supported this association (7,8). Here, we report an additional patient who has NSF that had previous multiple exposures to gadodiamide and had rapid improvement of this condition with the use of intravenous sodium thiosulfate (STS), an agent that has recently gained favor in the treatment of calciphylaxis.

## Materials and Methods

### *Patient*

A 26-yr-old white woman who had end-stage renal disease (secondary to Henoch-Schönlein purpura) and was on hemo-

dialysis (Table 1) presented with a history of severe pain (sharp, aching, throbbing) in her lower extremities for approximately 1 year with tightness, itching, joint stiffness, skin discoloration, and tenderness that began in January to February 2004. On examination, the patient was found to have yellowish scleral plaques bilaterally and lower extremities with hairless, shiny skin with bluish-brown discoloration and woody induration (Figure 1). Clubbing in both lower and upper extremities and sclerodactyly of the upper extremities (Figure 2) were also noted. These findings were reported to be insidious in onset by the patient.

During the course of the next several months, further diagnostic work-up was done (Tables 1 and 2). The patient was treated with large dosages of narcotics and gabapentin with minimal improvement of pain.

The patient was noted to have diffuse large arterial calcification on x-rays, and in view of this and the unresolved pain, a trial of intravenous STS was started (12.5 g three times a week at the end of hemodialysis) in May 2006. The patient tolerated the treatment well, with significant improvement in skin discoloration, pain, and joint stiffness within one month. The improvement in pain was remarkable to the extent that the patient's narcotic analgesic requirements became minimal and the skin discoloration was notably better. A skin biopsy was later obtained in July 2006, which confirmed the diagnosis of NSF (Figure 3). No histologic evidence of calciphylaxis was noted on the biopsy.

The patient's STS therapy was subsequently stopped in late August 2006 in view of her prolonged and complicated hospitalization for septic shock secondary to hemodialysis catheter-related infection. STS therapy has been reinstated now, and a repeat biopsy is being considered.

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Table 1. Medical history, medications, and pertinent laboratory tests<sup>a</sup>

| Laboratory Tests                           | History   | Medications (1/06)  |
|--|---|---|
| Lupus anticoagulant, negative              | Henoch-Schönlein purpura leading to ESRD  | Aspirin 81 mg/d   |
| Protein c and s, normal                    | Failed cadaveric renal transplant   | Colace 100 mg orally twice a day                              |
| Anticardiolipin Ab (IgG and IgM), negative | Secondary hyperparathyroidism and renal osteodystrophy with numerous related fractures  | Nephrocaps 1 tab daily  |
| Anti-ENA Ab, negative                      | Extensive posterior cervical spinal fusion involving T8 to L4, with prosthesis  | Cinacalcet 60 mg/d orally                                     |
| Anti-SM Ab, negative                       | Heparin antibodies  | Flexeril 10 mg orally twice a day                             |
| Anti-PM-1 Ab, negative                     | Peritoneal dialysis initially for 4.5 yr  | Ranitidine 150 mg orally twice a day                          |
| Anti-SSA/RO Ab, Anti-SSB/La Ab, negative   | Hemodialysis (since 1994)   | Gabapentin 100 mg orally every 8 h                            |
| Anti-SCL 70 Ab, negative                   | Multiple procedures for hemodialysis access placement since 1994 (thrombectomy in December 2003, approximately 1 mo before development of symptoms) | Benadryl 25 mg orally every night as needed                   |
| Anti-Ds DNA Ab, negative                   | Occlusion of vascular access multiple times   | Renagel 4 caps three times a day with meals                   |
| ESR (6/03), 33 mm/h                        | Subclavian deep vein thrombosis   | Plavix 75 mg/d  |
| ESR (6/04) 10 mm/h                         |   | Ativan in the evening as needed                               |
| CRP (6/03), 1.7 mg/dl (0 to 0.9)           |   | Zoloft 25 mg orally every night                               |
| Iron (2/03), 42 μg/dl (37 to 170)          |   | Fentanyl patch 75 mg every 3 d                                |
| TIBC (2/03), 149 μg/dl (250 to 450)        |   | MSIR 30 mg orally every 4 h as needed for pain                |
| Ferritin (2/03), 891 ng/ml (12 to 114)     |   | Epogen 300 to 600 U/kg per wk                                 |
| Vitamin B <sub>12</sub> (2/03), 757 pg/ml  |   | Venofor 100 mg/wk intravenously                               |
| Intact PTH (7/06), 258 pg/ml (10 to 69)    |   | No history of use of angiotensin-converting enzyme inhibitors |

<sup>a</sup>Ab, antibody; CRP, C-reactive protein; DS, double-stranded; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; PTH, parathyroid hormone; SM, Smith; TIBC, total iron-binding capacity.

Retrospective review of the patient's medical record revealed exposure to multiple Gd<sup>3+</sup>-based MRI and an MR venogram in 2003, which could be temporally related to the development of skin changes (Table 3). The patient was also noted to have multiple vascular access surgeries. In relation to the development of her symptoms, the patient had an arteriovenous graft placed in the right groin in March 2003, for which she underwent thrombectomy in December 2003 (approximately 1 mo before her symptoms developed). Subsequently, this access failed and the patient had several tunneled and nontunneled dialysis catheters placed at multiple sites, all after her symptoms developed. Her current hemodialysis access is a tunneled femoral catheter. Hemodialysis was complicated by chronic hypotension; therefore, antihypertensive agents, including angiotensin-converting enzyme inhibitors, were not administered.

## Discussion

### Role of Gadodiamide in the Development of NSF

Gadodiamide (Omniscan; Amersham Health, Amersham, UK) is a nonradioactive contrast agent that is approved by the FDA for use in MRI. Since its introduction, gadodiamide has become accepted as a safe alternative to iodine-based contrast agents in patients with impaired kidney function (9,10) and is usually well tolerated except for a few minor adverse effects.

However, recent case reports have suggested an association between the use of gadodiamide and the development of NSF in patients with impaired kidney function. In a recent case series by Marckmann *et al.* (5), the delay from exposure to first sign of the disease was 2 to 75 days.

The normal elimination half-life of gadodiamide in healthy individuals is approximately 1.5 h and can be prolonged up to 10 to 60 h in patients with ESRD, especially when dialysis is delayed. The clearance of gadodiamide with peritoneal dialysis (69% after 22 days of continuous dialysis) is prolonged compared with its clearance in a single session of hemodialysis (65%) (11).

The stability of Gd<sup>3+</sup> depends on its being bound to a ligand (*e.g.*, diethylenetriaminepentaacetic acid). The adverse effect profile of gadodiamide is likely due to the *in vivo* dissociation of Gd-ligand complex into Gd<sup>3+</sup> ion and ligand (12). This process is accelerated in patients with renal failure because of a combination of metabolic acidosis and inadequate clearance of the Gd-ligand complex. Endogenous metals such as Zn<sup>2+</sup>, Cu<sup>2+</sup>, Ca<sup>2+</sup>, and Fe<sup>3+</sup> also destabilize the complex by transmetallation (a process of displacing Gd<sup>3+</sup> from its ligand by competitive binding), leading to its dissociation (12). Grobner (4), in a recent case report, suggested that acidosis might be an essential co-factor in the pathogenesis of NSF, but this was not the case



Figure 1. Shiny, discolored, woody skin (on inspection and palpation) seen in the patient with nephrogenic systemic fibrosis (NSF). This picture was taken approximately 1 to 1.5 mo after the initiation of sodium thiosulfate (STS) therapy.



Figure 2. Sclerodactyly and severe clubbing seen in the patient with NSF.

in the study by Marckmann *et al.* (5), as well as with our patient (Table 2).

The dissociated  $Gd^{3+}$  ion has poor solubility and could form *in vivo* precipitates of salts by chelating with anions such as phosphate (which is elevated in patients with renal failure), carbonate, and hydroxyl, with eventual deposition in various tissues, such as liver, bone, skin, muscle, and the interstitium (12). Two different sequences of pathophysiologic events, as a reaction to noxious agents (*e.g.*, tissue deposits of Gd), have

Table 2. Pertinent laboratory findings at the time of MRI exams<sup>a</sup>

| Date of MRI | Bicarbonate Level (mEq/L) | Phosphorus Level (g/dl) | Calcium Level (mg/dl) |
|-------------|---------------------------|-------------------------|-----------------------|
| 01/30/03    | 29                        | 5.2                     | 9.6                   |
| 06/07/03    | 27                        | 7.6                     | 10.2                  |
| 07/15/03    | 32                        | 6.4                     | 9.9                   |
| 08/01/03    | 29                        | Not done                | 9.8                   |
| 11/24/03    | 27                        | Not done                | 9.9                   |

<sup>a</sup>From January to February 2004, the average bicarbonate level was 26, and the average phosphorus level was 9. MRI, magnetic resonance imaging.

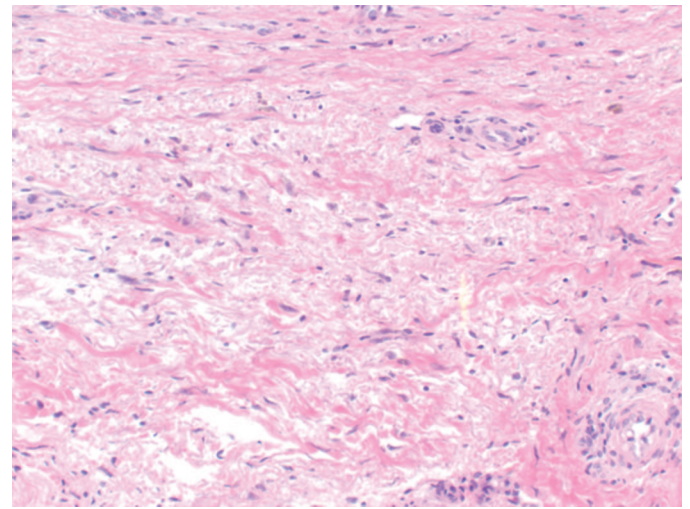


Figure 3. Thickened dermis with haphazardly arranged collagen bundles, increased dermal mucin, and scattered pigmented macrophages seen in a skin biopsy specimen in NSF. Biopsy was done approximately 1 to 1.5 mo after the initiation of STS therapy, with improvement in pain and skin changes.

been proposed in the development of NSF; the first hypothesis suggests possible infiltration of the affected tissues by  $CD68^{+}/XIIIa^{+}$  dendritic cells as a host response to noxious substances. These activated dendritic cells produce  $TGF-\beta$ , which not only initiates fibrosis but also enhances dendritic cell function, thereby initiating a vicious cycle of events that cause excess accumulation of dendritic cells in the affected tissues and extensive tissue fibrosis (13). A second hypothesis suggests the possibility that bone marrow–derived  $CD45RO^{+}/CD34^{+}/collagen\ I^{+}$  circulatory fibrocyte is released as a response to noxious stimuli in patients with NSF, resulting in fibrosis (14).

Recent case reports suggested development of NSF after administration of gadodiamide for MR angiography (which involves administration of gadodiamide at a dosage three times higher than the dosage approved by FDA for MRI in healthy patients), but our patient became symptomatic after repeated  $Gd^{3+}$ -based MRI exposures. This leads us to hypothesize a dosage-dependent effect of the association of gadodiamide with the development of NSF (G.S., personal observation).

Table 3. Timeline of MRI exams and onset of skin changes<sup>a</sup>

| 1/30/03  | 6/7/06                                       | 7/15/03                                   | 8/1/03                              | 11/24/03                            | January to February 2004 |
|--|--|---|-------------------------------------|-------------------------------------|--------------------------|
| →<br>MR venogram (to check patency of HD catheter) | →<br>MRI of lower extremities (R/O fracture) | →<br>MRI of pelvis/hips (R/O AVN of hips) | →<br>MRI pelvis/hips (R/O fracture) | →<br>MRI pelvis/hips (R/O fracture) | →<br>Skin/joint changes  |

<sup>a</sup>AVN, avascular necrosis; HD, hemodialysis; R/O, rule out.

Additional factors that have been postulated to contribute to the pathogenesis of NSF include large boluses of intravenous iron and recombinant epoetin (8,15). In addition to Gd<sup>3+</sup>, iron and other metal deposits have been described in skin specimens from patients with NSF. It is possible that the interactions between iron molecules and the ligand agent might contribute to the development of NSF. Our patient was receiving both epoetin (100 to 200 U/kg with each dialysis) and intravenous iron (100 mg/wk) in the months before and after the development of her symptoms.

Swaminathan *et al.* (15) found a higher median weekly epoetin dosage among case patients than control subjects (427 versus 198 U/kg). Of note, case patients had a higher serum ferritin and lower serum albumin (which was the case with our patient [Table 1]) than control subjects, suggesting chronic inflammation and decreased epoetin responsiveness. Although it is conceivable that the epoetin itself could be contributing to the development of NSF, another hypothesis is that patients with chronic inflammation have significantly greater endothelial dysfunction, leading to the extravascular accumulation of gadodiamide and leading to NSF. Alternatively, chronic inflammation may result in an accelerated fibrotic response. Here, higher dosages of epoetin may simply be a manifestation of resistance to epoetin secondary to the inflammation.

*Possible Mechanism of Action of STS in NSF*

STS (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>) is a white crystalline substance that has reducing/antioxidant and chelating properties with multiple uses, including photography, treatment of cyanide poisoning,

prevention of carboplatin-related (16) and cisplatin-related (17) toxicity, and most recently in the treatment of calciphylaxis (18,19). We propose yet another potential use of STS in the treatment of the debilitating disease NSF.

STS has FDA-labeled indications for the treatment of acne, Tinea versicolor, and cyanide poisoning, but other uses are off-label. Available evidence from human studies suggests that it is a safe drug with minimal adverse effects at the dosages currently used. The most common adverse effects are nausea and vomiting (usually during the infusion). Usual dosages are 12.5 to 25 g with every dialysis.

It is important to realize that both calciphylaxis and NFD can be present in the same patients, as described in a study by Edsall *et al.* (20). Association between metastatic calcification and NSF has also been described in many studies (3,21–23). TGF-β/Smad signaling cascades have been proposed as common factors in the pathogenesis of both of these conditions (*i.e.*, fibrosis in NSF and calcification in calciphylaxis/metastatic calcification [20]). Therefore, it is possible that there is a similar mechanism of action of STS in both NFD and calciphylaxis, but further studies are needed to establish this relationship.

The beneficial effect of STS in our patient was rather dramatic with marked improvement in pain and skin changes after the first few treatments. We hypothesized that the beneficial effects of STS could be due to its chelating and antioxidant properties (Table 4).

It is possible that STS may chelate Gd<sup>3+</sup>, like other cations, and enhance its solubility and stability in serum, thereby facil-

Table 4. Reactions showing the chelating and antioxidant properties of STS<sup>a</sup>

| Equation 1: Reaction showing the chelating property of STS   |   |   |  |   |   |                          |
|--|---|---|--|---|---|--------------------------|
| 2Gd <sup>3+</sup>  | + | 3(S <sub>2</sub> O <sub>3</sub> ) <sup>2-</sup> | →  | Gd <sub>2</sub> (S <sub>2</sub> O <sub>3</sub> ) <sub>3</sub> |   |                          |
| Gadolinium cation  | + | Thiosulfate anion                               | →  | Gadolinium thiosulfate  |   |                          |
| Equation 2: Reaction showing the antioxidant property of STS |   |   |  |   |   |                          |
| 1GSSG  | + | 2Na <sub>2</sub> S <sub>2</sub> O <sub>3</sub>  | (5H <sub>2</sub> O <sub>2</sub> ) (O <sub>2</sub> <sup>-</sup> )<br>superoxide | 4NaHSO <sub>4</sub>   | + | 2GSH + 2H <sub>2</sub> O |
| Oxidized glutathione   | + | STS   | →  | sodium bisulfate  | + | glutathione              |
|  |   |   | →  | glutathione<br>oxireductase                                   |   |                          |

<sup>a</sup>STS, sodium thiosulfate.

itating its excretion during dialysis. If the  $Gd^{3+}$  precipitates in the tissue are the trigger for the fibrosis in NSF, then its removal may have helped ameliorate our patient's condition. The diffuse arterial calcification that was noted in our patient and the effect of STS in chelating cations including both  $Gd^{3+}$  and calcium could also explain the improvement in skin changes. However, the effects of STS occurred rapidly in our patient, a benefit that cannot be attributed solely to its chelating action.

$Gd^{3+}$  has been shown to accumulate in sites adjacent to recent endothelial trauma or inflammation, eventually leading to the worsening of endothelial dysfunction in patients who have chronic kidney disease or are on dialysis (which was the case with our patient) (24). STS could restore this endothelial dysfunction by its antioxidant properties (ability to donate electrons to pair unpaired free radicals), which has a positive effect on endothelial nitric oxide (eNO) synthase uncoupling and in the production of eNO (19). eNO has several positive effects in the maintenance of a healthy, normally functioning endothelium, including scavenging of reactive oxygen species, anti-inflammatory effect, fibrinolysis, and vasodilation. It is also likely that STS has the same beneficial effect in the neuronal vascular bed—the vasa nervorum and the endoneurium of the peripheral neuronal unit (25)—which may explain the rapid improvement of pain. The chelation of calcium/ $Gd^{3+}$  may also contribute to its beneficial effect; however, this is most likely a long-term effect.

## Conclusion

The cause and pathophysiology of NSF are still obscure, but multiple associations, including but not limited to recent vascular surgeries, high-dosage iron, and epoetin therapy, have been described in the literature. Some of these associations have been noted in our patient along with the temporal relation of multiple  $Gd^{3+}$ -based MRI exposures to the development of NSF. Recent literature suggests an association between gadodiamide exposure and the development of NSF, but the direct cause-effect relationship has not been proved conclusively. We also hypothesize a dosage-dependent association with exposure to gadodiamide in the development of NSF in functionally anephric patients. The beneficial effect of STS that was observed in our patient is also very encouraging and suggests a potential for its use in the treatment of this debilitating condition, for which an effective treatment modality has not been found yet.

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## Disclosures

None.

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See the editorial, "Nephrogenic Systemic Fibrosis, Kidney Disease, and Gadolinium: Is There a Link?" on pages

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