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

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Nephrogenic 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 l) 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 (Gd³⁺) has become the leading suspect. In this issue of the Clinical Journal of American Society of Nephrology, two articles describe Gd³⁺ 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 Gd³⁺ exposure. Yerram et al. (8) describe NSF in a patient who had ESRD and was exposed to multiple doses of Gd³⁺, suggesting dosage-related toxicity or requirement of another co-factor (in addition to Gd³⁺) to trigger NSF. Grobner (9) initially observed NSF in five patients with ESRD after Gd³⁺ 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 Gd³⁺ before the development of NSF (3). In a personal communication, Dr. Henrik Thomsen (Copenhagen University, Copenhagen, Denmark; December 12, 2006) noted that Gd³⁺-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 Gd³⁺ within tissues of five patients with NSF using scanning electron...
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 (macrocyclic versus linear) and chelate charge (ionic versus nonionic). Macrocyclic 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 macrocyclic 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\(^{3+}\) 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\(^{3+}\) 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\(^{3+}\) 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\(^{3+}\) exposure and then again the day after exposure to enhance Gd\(^{3+}\) elimination. Because peritoneal dialysis clears Gd\(^{3+}\) 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\(^{3+}\) exposure alone is insufficient. These recommendations are not evidence based but rather are derived purely from associative data on the NSF-Gd\(^{3+}\) 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\(^{3+}\) and improving endothelial function through its antioxidant effects. Because deposition of Gd\(^{3+}\) in tissues and “endothelial dysfunction” may be critical aspects of NSF, they are logical targets of therapy.

Disclosures

None.

References


See the related articles “Nephrogenic Systemic Fibrosis: A Population Study Examining the Relationship of Disease Development to Gadolinium Exposure,” on pages 264–267, 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 258–263.