

Nephrogenic Systemic Fibrosis: Is Gadolinium the Missing Piece to the Puzzle?

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GOAL

To understand nephrogenic systemic fibrosis (NSF) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the presentation of NSF.
2. Discuss the association of gadolinium contrast with NSF in patients with renal failure.
3. Identify factors related to the pathophysiology of NSF.

CME Test on page 427.

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New medical disorders arise infrequently, but nephrogenic systemic fibrosis (NSF) is one such entity. It exclusively affects patients with renal failure, resulting in debilitating progressive fibrosis of the skin and systemic organs. Although much work has been done elucidating the histopathologic

changes, a trigger has not been detected. Recently, case reports have implicated gadolinium (Gd) contrast agents as a potential etiology, prompting a health advisory from the US Food and Drug Administration (FDA) in June 2006. We discuss the literature regarding the effects of Gd on tissue and its potential relationship to the known histopathologic characteristics of NSF.

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Nephrogenic fibrosing dermopathy (NFD) is an acquired idiopathic disorder seen exclusively in patients with renal failure. It was first recognized in 1997 in a group of patients following

renal transplant.^{1,2} Symmetric, thickened, fibrotic skin with brawny hyperpigmentation develops and primarily affects the limbs, sparing the head and neck. Associated symptoms include flexion contracture, pain, paresthesia, and/or severe pruritus. Yellow palmar papules and yellow scleral plaques also have been described. Although fibrosis initially was observed in the skin, more recent evidence suggests that NFD is a systemic disorder with variable and still unclear degrees of end organ damage, particularly pulmonary fibrosis.³⁻⁷ In light of the systemic involvement and newly described, rapidly progressive, fatal cases of NFD, the name has been changed to nephrogenic systemic fibrosis (NSF).³

Since 1997, more than 200 cases have been compiled through the Yale University NSF Registry. All patients have the unifying diagnosis of renal failure, but the disease has been observed in patients independent of age, gender, dialysis history, kidney transplant status, or the underlying cause of renal failure.^{8,9} The majority of cases have been reported in the United States and Europe, but new cases are now being reported in non-Western populations.^{10,11}

Given the novelty of the disease and the limited number of cases, the etiology has been elusive; however, most new diseases have some iatrogenic component. Prior to onset, many patients with NSF experienced coagulation abnormalities, transplant rejection, or some type of vascular intervention. As a result, contrast agents became suspect. Grobner¹² reported 5 patients with NSF who had magnetic resonance imaging with gadolinium (Gd)-diethylenetriamine-penta-acetic acid (DTPA) contrast 2 to 4 weeks prior to the onset of fibrosis. All of the patients with NSF were acidotic, in contrast to a similar unaffected group of patients with normal acid-base status.¹² Shortly after, Marckmann et al¹³ published a case series of 13 patients who developed NSF, all within 75 days of Gd contrast exposure; however, there was no correlation with metabolic acidosis in this study. Additional cases have been reported in association with exposure to Gd contrast.^{14,15} More recently, using electron microscopy with electron dispersion spectroscopy, Gd has been detected in the tissue of some patients with NSF.^{14,15} On June 8, 2006, the US Food and Drug Administration (FDA) released a public health advisory warning patients and physicians of the possible link between Gd-containing contrast agents and NSF.¹⁶ We report another case of NSF associated with Gd-DTPA exposure and propose a plausible explanation for the possible association and pathophysiology of NSF.

Case Report

A 54-year-old man with end-stage diabetic nephropathy status post-renal transplant was evaluated for

induration and thickening of the skin. Two months prior, he presented with an infected nonhealing ulcer of the left foot and was admitted to the hospital for intravenous antibiotics. During his hospital stay, he developed an acute exacerbation of his renal failure with a peak creatinine level of 6.7 mg/dL (an increase from his baseline [2–3 mg/dL; reference range, 0.6–1.2 mg/dL]). Evaluation of the ulcer of the lower extremity included Gd-DTPA-enhanced magnetic resonance angiography (MRA) vascular imaging. The day of MRA evaluation, his bicarbonate level was low at 15 mmol/L (reference range, 21–28 mmol/L), his creatinine level was elevated at 4.4 mg/dL, his corrected calcium level was within reference range, and his phosphate level was elevated at 6.1 mg/dL (reference range, 2.5–4.5 mg/dL). The patient's renal status continued to decline over the next several days and hemodialysis was initiated. The patient recalled progressive firmness of the skin, which presented approximately 4 to 6 weeks after his Gd-DTPA exposure. He denied pain, pruritus, or loss of sensation in the affected areas. At and around the time of presentation, the patient was taking calcitriol, calcium, dapsone, darbepoetin alfa, diphenoxylate hydrochloride and atropine sulfate, guar gum, magnesium, metoprolol succinate, mycophenolate mofetil, pantoprazole sodium, prednisone, psyllium, simvastatin, tacrolimus, and warfarin sodium. He was not on an angiotensin-converting enzyme inhibitor. Physical examination revealed subtle erythema overlying woody induration of the skin extending from the bilateral mid upper arms to the hands and from the bilateral mid calves to the anterolateral thighs and flanks, with substantially reduced range of motion in the hands (Figures 1 and 2). Findings from a biopsy specimen showed an increase in cellularity of the dermis, thickened collagen bundles, and subcutaneous septae. Many cells had poorly defined cytoplasm and elongated, plump, enlarged nuclei. Evaluation with elastin stains showed thickened elastic fibers in the dermis. Alcian blue staining revealed an increase in mucin in the dermis and subcutaneous septae consistent with NSF.

Comment

Our patient, like previously described patients,¹² had received Gd-DTPA for an MRA a few weeks prior to the onset of NSF. Grobner¹² also demonstrated that all of the patients with NSF were acidotic, in contrast to a similar unaffected group of patients with normal acid-base status. At the time of Gd-contrast exposure, we can infer that our patient likely had metabolic acidosis based on his bicarbonate level of 15 mmol/L. So the question remains: Is Gd exposure in the presence of a metabolic, or other unclear alteration, the trigger for this new and potentially lethal disorder?



Figure 1. There was a sharp line of demarcation on the left upper arm where the subtle red-brown woody induration of nephrogenic systemic fibrosis ended.



Figure 2. Subtle erythema overlying woody induration sparing the inguinal region was observed on the right lower extremity and abdomen.

Gadolinium is a rare toxic metal that, as a free ion, forms precipitates with anions, such as phosphate, carbonate, hydroxyl, or chloride, and can deposit in tissue.¹⁷ To reduce the toxicity, Gd contrast is chelated with other molecules (eg, DTPA) to form soluble ligand complexes, thus stabilizing it intravascularly. Stability is dependent on multiple parameters, including the thermodynamic stability constant, molecular kinetics, solubility constant, and selectivity constants.¹⁸ The half-life of chelated

Gd is approximately 1.5 to 2 hours and demonstrates a 500-fold increase in renal excretion when compared with elemental Gd.¹⁷ In the healthy kidney, approximately 90% of injected Gd-DTPA is excreted in the first 24 hours. However, in cases of renal failure, the half-life of Gd can be more than 30 hours.^{19,20} Prompt hemodialysis can help clear Gd, with average excretory rates of 78.2% after the first session and up to 99.5% after a fourth session.²⁰

There are 5 Gd-based contrast agents available for clinical use in the United States; however, none have been approved by the FDA for use in MRA.¹⁶ The stability of the agents has been studied in vitro and on animal models with healthy kidney function, but stability has not been evaluated in vivo in the setting of renal failure. All of the agents use chelators with very high affinity for Gd ion, but free ion can still be released in the presence of high concentrations of competing ions (metals or acids) or with prolonged exposure.^{17,19,21} Gadodiamide is the agent that has been used in the majority of patients with NSF reported in the literature, but it is too early at this time to implicate one agent over another and the FDA continues to investigate all Gd-based contrast agents as potential causes of NSF.^{12-14,16,18}

Gadolinium contrast was first approved for clinical use in magnetic resonance imaging in 1988.¹² In 1996, its use was favorably reported in patients with renal insufficiency.²² Since 1996, the use of Gd in patients with renal insufficiency has increased in frequency for vascular procedures such as aortography, dialysis fistulography, and renal angiography,¹⁷ which correlates well with the initial reports of NSF in 1997 in the United States and Europe.² Delayed adaptation of this imaging technique could explain the later presentation of NSF in non-Western countries.

Although the timing may correlate, how can one explain the possible pathophysiologic link between Gd and NSF? The histopathologic findings of NSF include thickened collagen bundles with surrounding clefts and a variable increase in mucin and elastic fibers. Immunohistochemistry reveals an increased proliferation of CD34⁺ fibrocytes, which are bone marrow-derived cells that circulate intravascularly and are thought to play a major role in wound healing.^{23,25} There is increased staining of CD34⁺/procollagen I⁺ circulating fibrocytes, transforming growth factor β 1, CD68⁺/factor XIIIa⁺ monocytes, and multinucleated giant cells.^{12,23,24} In addition, 2 separate groups have detected Gd in the tissue of patients with NSF.^{14,15} The first group detected Gd particles in 4 of 13 tissue specimens from 7 patients using electron dispersion spectroscopy. In addition, they noted the Gd particles were likely to be associated with macrophages.¹⁴ These results

were reproduced in a case report of a patient by Boyd et al.¹⁵ It is currently hypothesized that the deposition of CD34⁺/procollagen I⁺ circulating fibrocytes plays a major role in the pathophysiology of the disease, but the exact trigger, to this point, has been unclear.^{3,9} It now appears that Gd also plays a central role in the pathogenesis of NSF.

Wound healing is similar in any tissue that has undergone injury and occurs through a stepwise process of inflammation, proliferation, and remodeling. Studies have looked at the role of macrophages in liver injury using a rat model and gadolinium chloride hexahydrate (GdCl₃) to inhibit hepatic macrophages (Kupffer cells).²⁶ The current hypothesis is that hepatic injury activates macrophages, resulting in release of proinflammatory cytokines and the subsequent recruitment of systemic macrophages and myofibrocytes.²⁶ With inflammation, a profibrotic response occurs with deposition of types I and III collagen by fibrocytes. During the proliferation and remodeling phases, there is a systematic reversal of many of the cellular and molecular alterations of the inflammatory phase, which is essential to the restoration of healthy liver architecture and function.²⁶ The Kupffer cells are thought to be integral to the repair process via cytokine-mediated paracrine or cell-to-cell stimulus that causes regression of myofibroblasts and degradation of excess collagen with matrix metalloproteinases.

Prior experiments have revealed GdCl₃-induced macrophage toxicity.²⁷ It is speculated that elemental Gd is turbid above a pH of 6.0 and is engulfed

by macrophages. The Gd aggregates may again dissolve in the acidic environment of the endosomes and attach to components of the vesicle membrane. Recycling of endosomes to the plasma membrane may gradually change the cellular membrane causing cell death.²⁷ With the use of GdCl₃, Roggin et al²⁶ selectively inhibited Kupffer cells and observed delayed injury repair with increased extracellular matrix, bridging fibrosis and altered collagen metabolism, including increased type I collagen over time in livers of Gd-treated rats compared with the saline-treated controls.

In addition, it is believed that fibrocytes undergo several phenotypic changes over the course of wound healing, resulting in modification of their interactions with the surrounding extracellular matrix.²⁸ In 2004, Mori et al²⁵ used a mouse model to show that more than 60% of the circulating bone marrow-derived CD13⁺/collagen I⁺/CD45⁺/CD34⁺ fibrocytes that migrate to sites of tissue injury become α -smooth muscle actin-positive myofibroblasts by day 7 post-wound healing. They noted down-regulation of expression of CD34 as cells underwent differentiation to myofibroblasts. They concluded that circulating fibrocytes undergo rapid phenotypic change under the influence of local factors once they have migrated to sites of injury.²⁵

Based on these previously reported data, we hypothesize that in the presence of some unclear metabolic alteration, such as acidosis, and renal failure, exposure to high-dose Gd (as in MRA)

Summary of Key Points: Gadolinium and Nephrogenic Systemic Fibrosis (NSF)

- Nephrogenic systemic fibrosis is seen exclusively in patients with renal failure,^{8,9} a patient population predisposed to metabolic abnormalities and impaired contrast clearance.
- Gadolinium can disassociate from its chelator in the setting of prolonged exposure, acidosis, or anion excess.^{17,19,21}
- Gadolinium has been demonstrated in tissue of patients with NSF associated with macrophages,^{14,15} which are seen in early NSF histopathology.
- Gadolinium is known to induce macrophage toxicity in rats, causing increased type I collagen deposition.²⁶
- Bone marrow-derived CD34⁺ fibrocytes migrate to sites of tissue injury and are seen in NSF.²³⁻²⁵
- Macrophages are crucial for proper wound healing at sites of tissue injury and progression through the remodeling phase.²⁶
- Gadolinium was first used in high doses for magnetic resonance angiography in 1996.²²
- Nephrogenic systemic fibrosis was first recognized in 1997.^{1,2}

for prolonged periods of time could result in Gd ion dissociation from its chelator. The Gd ion may precipitate with other anions, such as phosphate, or other metals, such as iron, and deposit in any tissue, resulting in local macrophage recruitment to engulf the elemental Gd. This theory could explain the initial tissue injury and the presence of multinucleated giant cells. The macrophages could recruit proinflammatory cells, such as CD34⁺ fibrocytes; however, the elemental Gd may cause early macrophage death, as previously demonstrated.²⁷ The loss of macrophages could result in an aberrant tissue injury response with failure to progress to the remodeling stage. The persistent proinflammatory/recruitment stage with loss of functional macrophages could explain the high proportion of CD34⁺ fibrocytes, as they lack macrophage-derived stimulus to undergo appropriate phenotypic/functional change. Ultimately, we propose that NSF may stem from elemental Gd-induced macrophage death (Table).

Although there appears to be a strong association between Gd exposure and NSF, potential triggers are still being evaluated. In the past decade, there has been a dramatic shift to the use of MRA with Gd contrast in patients with renal failure due to known contrast-induced nephropathy observed with iodinated contrast. Considering the number of patients with renal failure receiving Gd contrast, Gd exposure alone is unlikely to be the sole cause of NSF and is more likely a component in a multifactorial process; however, the other risk factors remain elusive. MRA technology has been lifesaving for many patients with renal failure and remains a medical necessity in many situations, but the possible link to NSF may result in a need to modify current medical practices. The FDA's public health advisory strongly recommends prompt initiation of dialysis in any patient with advanced kidney disease who undergoes MRA with Gd.¹⁶ With the potential association of the dissociation of Gd chelates in an acidic environment, it also may be prudent to consider normalizing the pH of patients with bicarbonate infusion prior to MRA. At this time, further studies evaluating the safety of Gd contrast, its possible link to NSF, and the possible role of macrophage inhibition in the pathophysiology of NSF are needed.

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