MRI Safety Update 2008: Part 1, MRI Contrast Agents and Nephrogenic Systemic Fibrosis

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OBJECTIVE. This article is the first part of a two-part series on MRI safety. In this article, part 1, the topic of MRI contrast agents and nephrogenic systemic fibrosis (NSF) is addressed.

CONCLUSION. To prevent incidents and accidents associated with MRI, it is necessary to regularly revisit the safety topics that directly impact patient management especially with respect to the subjects that are "new" (e.g., MRI contrast agents and NSF), those that should be reassessed because of recent changes, topics that deserve emphasis because of controversy or confusion, and information that should be considered in light of new findings.

Keywords: 3-T MRI, devices, gadolinium-based contrast agents, implants, MRI artifacts, MRI contrast agents, MRI safety, nephrogenic systemic fibrosis

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In consideration of the constant evolution of issues related to MRI safety and the need to update and revise existing guidelines and policies and procedures, there is an ongoing challenge to be aware of the latest developments associated with this topic. Notably, comprehensive reviews and textbooks have been written on the subject of MRI safety and there are Websites with content that is updated on a regular basis [1–15]. Therefore, the reader is referred to those important resources. The goal of this article is to provide an MRI safety update that covers selected topics including those that are "new" (e.g., MRI contrast agents and nephrogenic systemic fibrosis [NSF]), subjects that should be reassessed because of recent changes (e.g., screening patients and individuals), topics that deserve emphasis because of controversy or confusion (e.g., certain policies and procedures), and information that should be considered in light of new findings (e.g., MRI test results for implants and devices, including items evaluated at 3 T).

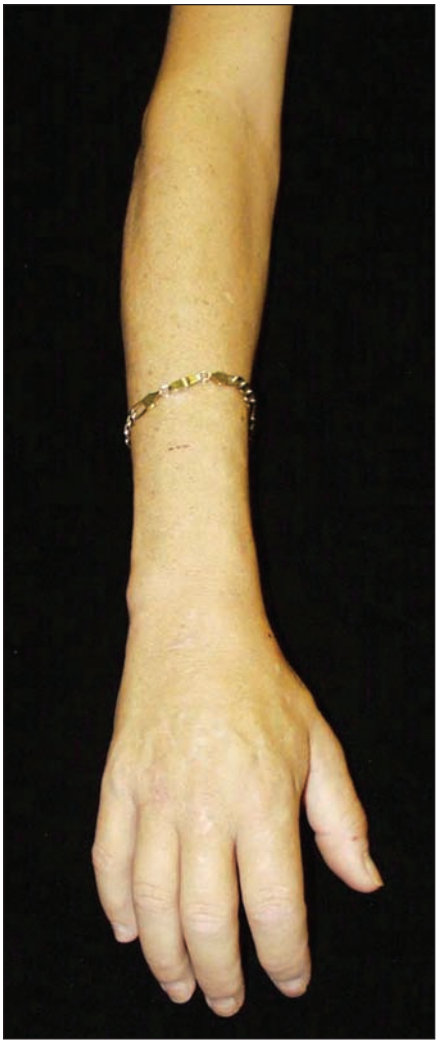
This article is part 1 of a two-part series on MRI safety. In this article, the topic of MRI contrast agents and NSF is addressed.

NSF: Facts, Hypotheses, and Preventive Measures

Even though the first cases of NSF were identified in 1997 and the first published report of 14 cases appeared in 2000 [16], NSF has received great attention only recently, especially because of its possible association with exposure to gadolinium-based contrast agents (GBCAs), commonly and widely used in MRI for the past 20 years. "Nephrogenic" does not mean that the disease is caused by factors originating in the kidney, but that NSF has been observed only in patients with chronic kidney disease, and "systemic" emphasizes the systemic nature of this fibrosing disorder [17]. NSF was previously known as "nephrogenic fibrosing dermopathy" because its most prominent and visible effects are observed in the skin where the histopathologic findings closely parallel those observed in wound-healing reactions [16, 18–20]. The nomenclature of the disease has been changed to "NSF" based on autopsy case reports of individual NSF patients that have reported variable degrees of myocardial, pericardial, and pleural fibrosis, along with the involvement of nerves and skeletal muscles [21–23].

Diagnosis of NSF

NSF cannot be detected using a single diagnostic test. A confident diagnosis can usually be reached through the combination of a clinical history, a physical examination, and the histopathologic assessment of a biopsy specimen of involved skin. The physical examination should be performed by an experienced dermatologist or rheumatologist, and the biopsy specimen should be examined by an experienced dermatopathologist. The



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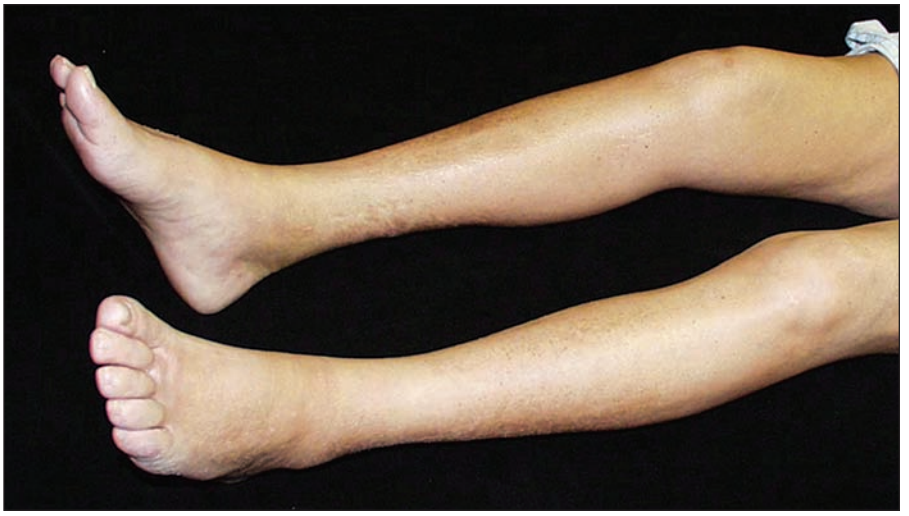

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Fig. 1—Cutaneous changes of nephrogenic systemic fibrosis (NSF).
A and **B,** Photographs show cutaneous changes of NSF with brawny hyperpigmentation and tethering of skin on arms and legs resulting in flexion contractures of the fingers, elbows, and knees. (Reprinted with permission of John Wiley & Sons, Inc. [129]; Kay J. What causes nephrogenic systemic fibrosis? *The Rheumatologist* 2007; 9:18–20; courtesy of Jonathan Kay, Massachusetts General Hospital and Harvard Medical School, Boston, MA)

main elements that should guide physicians in the diagnostic process are the clinical presentation in the setting of severe renal insufficiency and confirmatory cutaneous histopathologic findings [24].

To date, NSF has been observed only in patients either with acute or chronic severe renal insufficiency (glomerular filtration rate [GFR] < 30 mL/min/1.73 m^2) or with acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period [24]. Most patients with NSF have a GFR < 15 mL/min/1.73 m^2 and are receiving (or have received) either hemodialysis or peritoneal dialysis or both [24].

The skin changes caused by NSF can mimic progressive systemic sclerosis with a predilection for extremity involvement that can extend to the torso. Unlike scleroderma, NSF usually spares the face. Skin lesions usually begin with swelling, progressing to erythematous papules and coalescing violaceous to hyperpigmented, brawny plaques with follicular dimpling (peau d'orange) changes (Figs. 1 and 2). Peripheral irregular fingerlike or ameboid projections may be present along with islands of sparing. Bullae and nodules have also been reported. Skin involvement is often symmetric and bilateral (Figs. 2 and 3). New onset white-yellow scleral plaques with dilated capillary loops have been noted in several patients and may be suggestive of NSF especially if they are observed in patients younger than 45 years old [16, 19, 24, 25].

The involved skin and subcutis can become markedly thickened and hardened, unpinchable, with a wooden consistency to palpation. The induration characteristically involves the distal extremities first, gradually proceeding to involve the proximal extremities to the level of the mid thigh and mid upper arms where it may show a pattern of bumpiness [16, 24, 25] (Fig. 4). Involvement of the skin and subcutis overlying joints can cause a decrease in function of the hands and feet first and then of more proximal joints in the affected extremities, so patients may become wheelchair-dependent. Joint contractures may be accompanied by edema of the fingers, wrists, toes, and ankles (Fig. 5).

If renal function is restored, the skin lesions may stabilize or even regress [24]. Some patients (estimated at < 5%) develop rapidly progressive, fulminant NSF associated with an accelerated loss of mobility and severe pain [24, 25]. Patients with NSF may complain of itching and sharp pain that may be localized in the affected areas, in the rib cage, or the hips. Loss of appetite, paresthesia, and muscle weakness are also described [24, 25].

If the signs and symptoms noted are observed in patients with severe renal insufficiency, a biopsy should be performed to obtain specimens of involved skin. A deep punch biopsy of at least 3 mm may reveal sufficient findings to confirm the diagnosis. However, it is always better to obtain deeper biopsy specimens because the disease characteristically extends along fibrous septa into subcutaneous fat and fascia and sometimes into underlying skeletal muscle [24].

Histologically, NSF is characterized by dermal fibrosis and may be histologically indistinguishable from scleromyxedema. The two entities can be reliably distinguished only by clinicopathologic correlation [26]. In NSF, there is always an increased number of fibrocytes that are CD34-positive and procollagen I–positive when stained immunohistochemically [26] (Fig. 6). This dual positivity is characteristic of so-called "circulating fibrocytes," mesenchymal stem cells of bone marrow origin that participate in wound repair [26, 27].

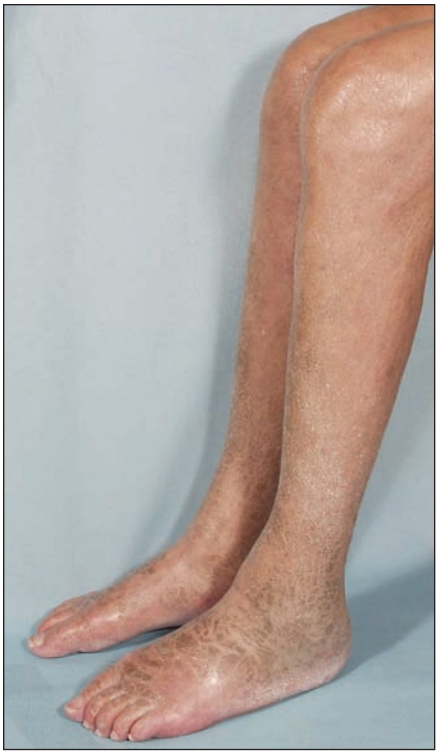

Fig. 2—Photograph shows hyperpigmented, brawny plaques with skin induration and flexion contractures of fingers, ankles, and knees accompanied by edema of fingers in 35-year-old woman with nephrogenic systemic fibrosis. (Reprinted with permission of [130]; Thomsen HS. Nephrogenic systemic fibrosis. *Imaging Decisions* 2008; 11:13–18; courtesy of Henrik S. Thomsen, Copenhagen University Hospital, Herlev, Denmark)

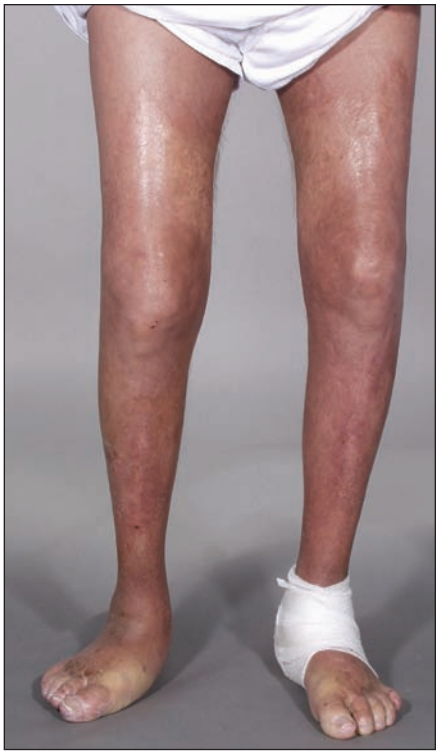

Fig. 3—Photograph shows late stage of nephrogenic systemic fibrosis in patient with plaques and skin induration of both legs up to thighs and flexion contractures. Skin involvement is symmetric and bilateral. Affected skin is hairless, sclerotic, and brown. (Reprinted with permission of [67]; Khurram M, Skov L, Rossen K, Thomsen HS, Marckmann P. Nephrogenic systemic fibrosis: a serious iatrogenic disease of renal failure patients. *Scand J Urol Nephrol* 2007; 41:565–566; courtesy of Henrik S. Thomsen, Copenhagen University Hospital, Herlev, Denmark [www.informaworld.com/suro])

In early lesions of NSF, collagen bundles may be quite narrow, with abundant edema fluid or mucin separating them. Procollagen I positivity is already present, but is noted inconspicuously in the perinuclear cytoplasm of the bland dermal fibrocytes. In more advanced disease, collagen bundles become thicker, still generally maintaining clefts of separation between their neighbors, and the cytoplasm of the fibrocytes becomes plump and intensely procollagen I-positive [28] (Fig. 7). The dermis is always involved by the histopathologic pattern noted above, whereas the epidermis is not typically affected by NSF, although some degree of basilar pigmentation and epidermal acanthosis may be noted in advanced disease [28]. The subcutaneous septa are markedly widened and in these deeper NSF foci, the widened septa are collagenized in the same manner as described above [28].

Other occasional findings may be a combination of epithelioid CD68-positive histiocytes in the subcutaneous septa, multinucleated giant cells, osteoclastlike giant cells, foci of osteoid deposition, or calcified bone spicules [28]. Increased numbers of factor XIIIa–positive dendritic cells or coexpression of factor XIIIa and CD68 in the same cell has been observed as well. Vascularity is not typically prominent, although some cases of NSF show evidence of angiogenesis. Microthrombi and vasculitis have never been observed [28]. The fibrotic process may extend through the fascia and into the underlying skeletal muscle [28]. The main criteria to make a confident diagnosis of NSF are shown in Appendix 1.

What We Currently Know About NSF

As we noted earlier, NSF has occurred only in patients with severe or end-stage renal failure, acute or chronic. NSF appears to affect males and females in approximately equal numbers [25, 29]. It has been confirmed in children and elderly adults, but tends to affect middle-aged adults most commonly [25, 27, 30, 31] and has been identified in patients from a variety of ethnic backgrounds and from North America, Europe, and Asia [27, 32]. Recent reports have strongly correlated the development of NSF with exposure to GBCAs used in MRI [33–35].

NSF cases occurring after the sole administration of one GBCA are defined as "unconfounded." If a case of NSF follows the administration of two or more agents, it is more difficult to determine which agent is associated with the development of the disorder, and the case is reported as "confounded" [34]. NSF cases may be spontaneously reported by health care professionals or by consumers to the health care authorities or may be found in peer-reviewed articles [22, 36–81]. Several spontaneous reports are not biopsy-proven and duplications of the same report are possible. The quality of the information on

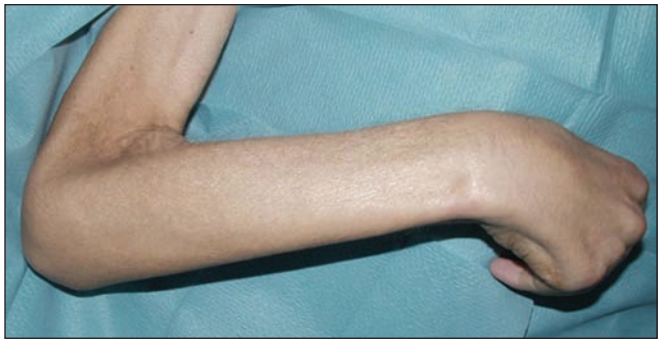

Fig. 4—Photograph shows plaques of nephrogenic systemic fibrosis in patient with follicular dimpling changes and severe contractures of elbow, wrist, and fingers. (Reprinted with permission of [130]; Thomsen HS. Nephrogenic systemic fibrosis. *Imaging Decisions* 2008; 11:13–18; courtesy of Henrik S. Thomsen, Copenhagen University Hospital, Herlev, Denmark)

NSF cases reported in peer-reviewed articles is usually more reliable even if a few cases are not biopsy-proven [64] or the names of the GBCAs involved in the NSF cases are not always reported. Renal disease has always pre-dated or occurred concurrently with GBCA administration [24]. Most biopsy-proven NSF cases have occurred:

- in the first 6 months after the last exposure to GBCAs. However, some reports suggest that the development of NSF may occur later, even several years after the exposure to a GBCA [22, 36–82];
- after single high doses of GBCAs or, more commonly, after repeated contrast-enhanced MRI examinations performed in a relatively short period of time (days to 6 months) [36, 37, 43, 52, 82, 83];
- in patients with end-stage renal disease (Table 1); and
- after the administration of gadodiamide (Omniscan, GE Healthcare; Fig. 8). The odds ratio for developing NSF after gadodiamide exposure was reported to be 22.3 and 32.5 in two different studies [37, 43].

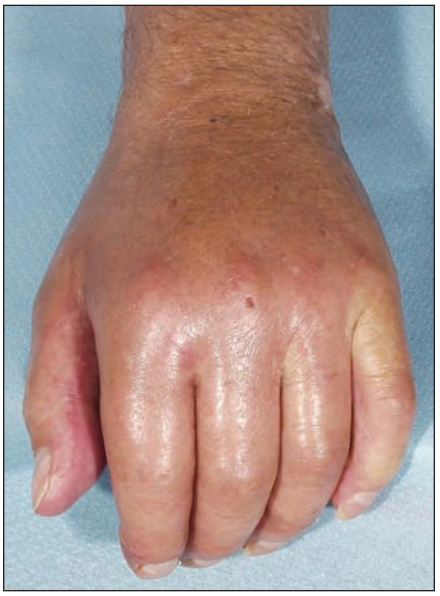

Fig. 5—Hyperpigmented, brawny plaques and flexion contractures of wrist and fingers accompanied by edema of fingers in patient with nephrogenic systemic fibrosis. Courtesy of Henrik S. Thomsen, Copenhagen University Hospital, Herlev, Denmark)

The second highest number of unconfounded cases has been observed after the administration of gadopentetate dimeglumine (Magnevist, Bayer Healthcare) [47, 61, 63, 64]. No literature exists about unconfounded cases with gadobenate dimeglumine (MultiHance, Bracco Diagnostics) or gadoteridol (ProHance, Bracco Diagnostics). Only three cases of NSF are reported as confounded in peer-reviewed articles: one after gadobenate dimeglumine and gadodiamide administration [42], one after gadopentetate dimeglumine and gadobenate dimeglumine administration [63], and one after multiple gadodiamide, gadopentetate, gadoterate dimeglumine (Dotarem, Guerbet) administrations [72]. The confounded case reported by Othersen et al. [63] was actually an unconfounded case after the sole administration of gadopentetate dimeglumine [84]. Recently, Broome [85] completed an analysis and summary of the medical literature and contacted the authors of case reports to clarify which GBCA was associated with NSF cases when a specific agent was not reported in the original article or in follow-up letters. If several reports had originated from the same institution, the authors were contacted to avoid redundant reporting. According to the results of this extensive analysis, as of February 1, 2008, there were 190 biopsy-proven, unconfounded cases of NSF with the following associations: 157 gadodiamide, eight gadopentetate dimeglumine, three gadoversetamide (OptiMARK, Covidien), and 18 unspecified GBCAs. Four cases were confounded, and five had not been associated to any GBCA.

In several studies the incidence of NSF after exposure to gadodiamide has been reported to be between 3% and 7% [34, 37, 42, 43, 47, 52] and up to 18% in the high-risk group of patients with a GFR < 15 mL/min/1.73 m^2 [77]. No cases of NSF were observed in a group of 141 patients on hemodialysis and with 198 exposures to gadoteridol [78]. A relatively high incidence (30%) of NSF cases has been reported after

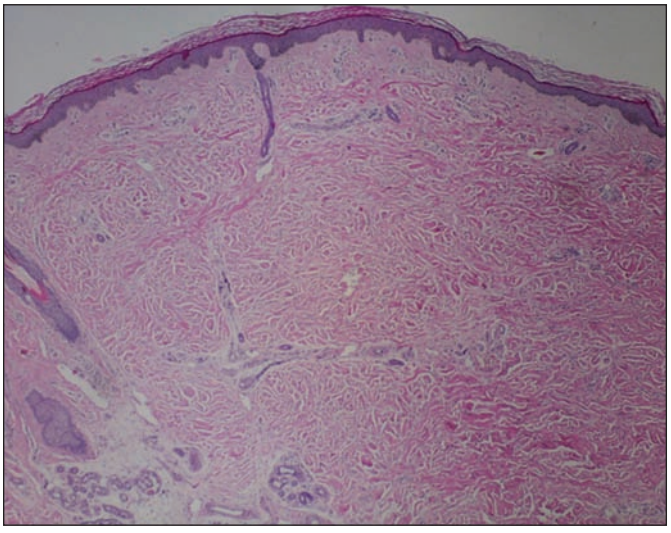

Fig. 6—Skin biopsy from skin of patient with nephrogenic systemic fibrosis. Photomicrograph shows CD34+ spindle or epithelioid cells in a reticular or parallel arrangement. (Reprinted with permission of [129]; Kay J. What causes nephrogenic systemic fibrosis? *The Rheumatologist* 2007; 9:18–20; courtesy of Jonathan Kay, Massachusetts General Hospital and Harvard Medical School, Boston, MA)

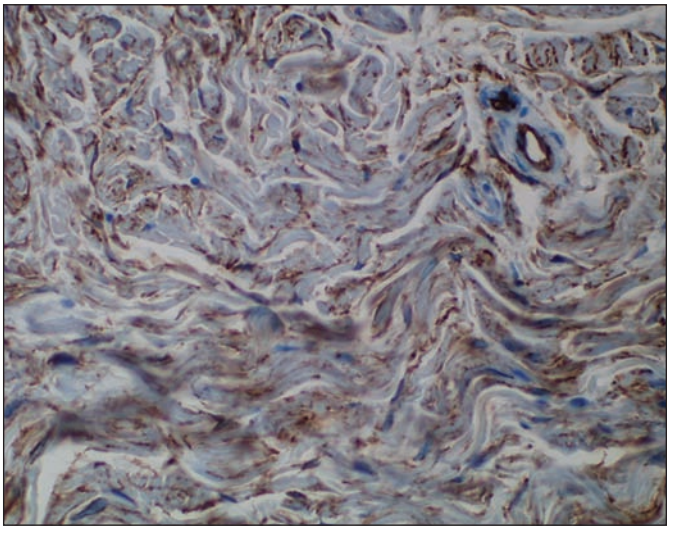

Fig. 7—Skin biopsy (H and E) from leg of patient with nephrogenic systemic fibrosis. Photomicrograph shows thick dermal collagen bundles surrounded by clefts with spindle cells intercalated between collagen bundles throughout reticular dermis. (Reprinted with permission of [129]; Kay J. What causes nephrogenic systemic fibrosis? *The Rheumatologist* 2007; 9:18–20; courtesy of Jonathan Kay, Massachusetts General Hospital and Harvard Medical School, Boston, MA)

TABLE 1: Number of Cases Reported in Peer-Reviewed Literature, Indicated by Severity of Renal Impairment

Severity of Renal Impairment	No. of Cases
GFR not reported	21
GFR between 15 and 29 mL/min/1.73 m^2	14
GFR < 15 mL/min/1.73 m^2	
On dialysis	143
Not on dialysis	31
Unknown	20

Note—Data are from [22, 36–81]. GFR = glomerular filtration rate.

administration of gadopentetate dimeglumine. However, most of those NSF cases were not biopsy-proven [64].

Open Issues: Tissue Deposition of Gadolinium—An Exogenous Trigger of NSF?

No case of NSF could be identified before 1997 [86]. This truly new disease entity should then result from exposure of patients with advanced renal failure to one or more new exogenous agents—that is, a new medication, toxin, or infectious agent or new ways of using previously existing medications [87]. The first suspects were exposure to high-dose erythropoietin and lack of angiotensin-converting enzyme inhibitor therapy in the presence of cofactors such as hypercoagulable states, various forms of vascular injury, vascular surgical procedures, and liver failure—in particular, hepatorenal syndrome and liver transplantation [24].

Since January 2006, when the study by Grobner [36] was published, gadolinium had become the prime suspect, even though GBCAs had been available for clinical use since the late 1980s—that is, at least 10 years before the first cases of NSF were identified.

The working hypothesis is that free gadolinium is released from the various chelates and stays for weeks, months, or even years in the skin and other tissues [24]. In the skin of patients with advanced renal failure, the gadolinium ion, maybe as a precipitate engulfed in a macrophage, attracts or activates circulating fibrocytes, bone marrow–derived cells that participate in normal wound healing and fibrosis and are believed to underlie aberrant fibrosis in NSF [24]. These cells are distinct from other fibrocytes in that they have a specific immunophenotype—that is, the CD34 and procollagen I dual–positive profile previously mentioned in this article while describing the histopathology hallmarks of NSF [27].

If free gadolinium triggers the disease, then the higher the amount of free gadolinium in the cutis, subcutis, and other tissues, the higher the risk of NSF. Four factors may favor the deposition of the gadolinium ion in the body: first, higher and longer-lasting circulating levels of GBCAs; second, the GBCA dose administered to at-risk patients; third, repeated exposures; and, fourth, the stability of the GBCA molecule. In patients with reduced kidney function, the elimination of GBCAs is markedly decreased [88–94], leading to prolonged elevated plasma concentrations of these compounds, especially after the injection of high GBCA doses, and to increased availability in the circulation of the source of gadolinium ions. The increased plasma concentration of gadolinium chelates, relative to that occurring in patients with normal renal function, would then tend to equilibrate among all the body's extracellular fluid compartments to the degree and rate allowed by the body's system of permeable and semipermeable membranes. Dialysis-dependent patients retain injected gadolinium chelate in their extracellular fluid volume until the next dialysis session. Until dialysis, most of the injected gadolinium chelate has the opportunity to equilibrate in the extracellular fluid compartment. At dialysis, a fractional removal of gadolinium occurs, thus incrementally reducing its plasma concentration [89, 95]. However, the entire molecule of the GBCAs and free gadolinium ions may stay for long time periods within the body. Indeed, it has been shown that gadolinium ions may be found in the skin of patients with impaired renal function up to 11 months after the administration of gadodiamide [35, 41]. Repeated exposures may favor the accumulation of gadolinium ions in the skin and other tissues, such as the bone and the liver [36, 96].

Finally, the amount of free gadolinium that may accumulate within the body depends on the amount of gadolinium ions released by the various chelates. That is, it is dependent on their ability to bind to and sequester the gadolinium ion. That ability is called "stability" and can be assessed in vitro [97–100] (Table 2) or, much better, in vivo [101]. In vivo dissociation of GBCAs into gadolinium ion and ligand can be facilitated by a number of endogenous metals, such as zinc, copper, calcium, and iron, all working simultaneously to destabilize the complex and leading to its dissociation. Stability data measured in vivo, such as rodent biodistribution data or even data from studies in humans, take all of these considerations into account [101]. Displacement of the gadolinium ion from its ligand by other

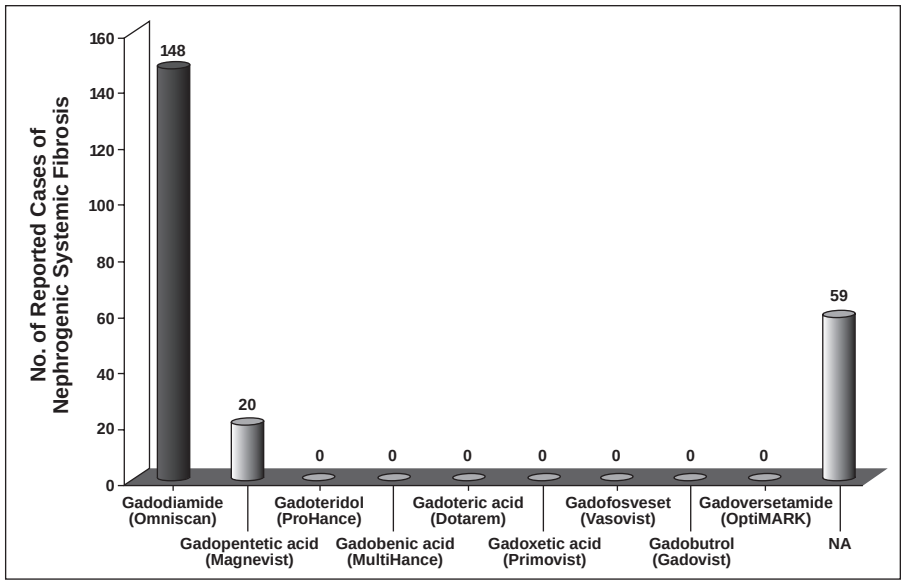

Fig. 8—Graph shows number of unconfounded cases of nephrogenic systemic fibrosis reported in peer-reviewed literature. Data are from [22, 36–81]. NA = name of contrast agent was not reported. Manufacturers of contrast agents: Omniscan, GE Healthcare; Magnevist, Bayer HealthCare; ProHance and MultiHance, Bracco Diagnostics; Gadovist, Vasovist, and Primovist, Bayer Schering Pharma; OptiMARK, Covidien; and Dotarem, Guerbet.

TABLE 2: Thermodynamic Stability Constants of the Gadolinium-Based MRI Contrast Agents Available in the United States and in Europe

Trade Name (Generic Name, Acronym)	Name of Manufacturer	Thermodynamic Stability Constant ($\log K_{therm}$, pH = 1.0)	Conditional Stability Constant ($\log K'$, pH = 7.4)	Free Chelating Agent in Solution (%)
Omniscan (gadodiamide, Gd-DTPA-BMA) [97, 98]	GE Healthcare	16.9	14.9	5.0
OptiMARK (gadoversetamide, Gd-DTPA-BMEA) [98]	Covidien	16.6	15.0	NA
Magnevist (gadopentetic acid, Gd-DTPA) [97, 98]	Bayer HealthCare	22.1	17.7	0.2
MultiHance (gadobenic acid, Gd-BOPTA) [98, 99]	Bracco Diagnostics	22.6	18.4	None
Primovist (gadoxetic acid, Gd-EOB-DTPA) [98, 99]	Bayer Schering Pharma	23.5	18.7	< 0.1
Vasovist (gadofosveset, MS-325) [100]	Bayer Schering Pharma	23.2	19.2	None
Dotarem (gadoteric acid, Gd-DOTA) [97, 98]	Guerbet	25.8	18.8	None
ProHance (gadoteridol, Gd-HP-DO3A) [97, 98]	Bracco Diagnostics	23.8	17.1	0.1
Gadovist (gadobutrol, Gd-BT-DO3A) [98]	Bayer Schering Pharma	21.8	NA	NA

Note—NA = not available.

metals through competitive ionic binding is known as transmetallation. The lower the stability of the GBCA, the more marked the displacement of the gadolinium ion from its ligand by the other metals [101, 102].

In renal failure, the combination of low chelate stability, high GBCA dose, and absence of adequate GBCA clearance may lead to increased deposition of the GBCA and free gadolinium in tissues, cutis and subcutis included [102, 103]. Notably, most NSF cases occurred in patients with a GFR < 15 mL/min/1.73 m^2, or in patients who received a high single dose or repeated GBCA doses, and most NSF cases were associated with the administration of gadodiamide, the GBCA with the lowest chelate stability among those available for clinical use [35, 102, 104]. Besides, metabolic acidosis, often present in patients with advanced renal failure, may favor clinically significant transmetallation because acidemia, resulting from inflammation or tissue hypoxia, may promote conversion of hemosiderin to iron donor, thus favoring the formation of iron–ligand complexes [105–107].

In support of the hypothesis that free gadolinium in tissues may trigger the development of the disease, the results of an animal study conducted by Bayer Healthcare showed NSF-like lesions were proportional to the release of gadolinium ion in the skin of the treated animals [108]. Against the theory that the release of gadolinium from GBCAs and its deposition in the skin may trigger the disease are the following: first, the fact the GBCAs were already widely used in renally impaired patients well before 1997—that is, before the first NSF case was identified; second, a few cases of NSF occurred in patients never exposed to GBCAs [109, 110]; and, third, Edward et al. [111] exposed fibroblasts to gadodiamide and gadolinium chloride and found that although gadodiamide stimulated fibroblast proliferation and hyaluronan synthesis in a dose-dependent manner, gadolinium chloride did not affect fibroblast growth.

Open Issues: Why Most Patients at Risk Do Not Develop NSF?

Most patients with GFR < 30 mL/min/1.73 m^2 do not develop NSF even if exposed to high doses of GBCAs [63, 102]. Other possible NSF triggers, cotriggers, or predisposing conditions have been suggested, such as a proinflammatory state, vascular surgery, hypercoagulability or thrombotic events, metabolic acidosis, and patient exposure to erythropoietin [24], even though there is no evidence that any of these conditions or drugs may play a role in the genesis of NSF. In essence, no one knows why only a minority of patients at risk develops NSF, so extreme caution should be exercised when administering GBCAs in all patients with advanced renal failure. Recently, caution has been recommended also in the treatment of renally impaired patients with lanthanum carbonate (Fosrenol, Shire US) in view of the fact that gadolinium and lanthanum, both lanthanides and trivalent cations, are close in the periodic table of Mendeleev [112]. Similar to gadolinium, lanthanum has a high affinity for phosphates, so it is used as a phosphate binder for the treatment of hyperphosphatemia in patients with end-stage renal failure—that is, in the patients who are at highest risk for NSF. In addition, lanthanum and gadolinium have analog physicochemical properties, so one may speculate that that lanthanum deposition in tissue may trigger NSF [112]. Although GBCAs are for single IV administration, lanthanum carbonate is given at oral doses up to 3.5 g per day for weeks or months. Even if the plasma concentrations of lanthanum during chronic treatment with lanthanum carbonate (between 0.35 and 0.78 mg/L) are much lower than that of gadolinium after GBCA IV injection [113], lanthanum progressively accumulates in tissues. No data are available about accumulation in skin, whereas in bone, the highest concentration observed in dialysis patients was 9.5 mcg/g of bone after 4.5 years of treatment with lanthanum carbonate [114]. After IV injection of a standard dose (0.1 mmol/kg) of gadoteridol or gadodiamide, gadolinium concentration in bone was 1.18 mcg/g of bone after the low-stability agent gadodiamide and 0.466 mcg/g of bone after macrocyclic gadoteridol [115]—that is, 8–20 times lower than that observed for Fosrenol after its chronic administration. Therefore, although a lot of attention has been given to gadolinium as a possible trigger of NSF, a possible role of lanthanum in the pathogenesis of NSF should be explored further.

How to Minimize the Risk of NSF

Step 1: Identify patients at risk—The first step to minimize the risk of NSF is to identify patients at risk for NSF—that is, those patients who have a GFR below 30 mL/min/1.73 m^2—independently of their age, race, or sex. The level of GFR should be estimated from prediction equations

that take into account the serum creatinine concentration and some or all of the following variables: age, sex, race, and body size [116]. The most widely used equations for adult patients are the Modification of Diet in Renal Disease (MDRD) Study equation [117] and the Cockcroft-Gault formula [118]. Even if both equations provide a marked improvement over serum creatinine alone [119], the MDRD Study equation may perform better than the Cockcroft-Gault formula, but the data are very limited [120–122]. Both prediction equations assume that the amount of creatinine produced by the patient is equal to the amount being removed by the kidneys. Therefore, both equations are not suitable if renal function is in an unstable condition—that is, in patients with acute renal failure or on dialysis. Results may also deviate from true values in patients with exceptional dietary intake (e.g., vegetarian diet, high protein diet, creatine supplements), extremes of body composition (e.g., very lean, obese, paraplegia), or severe liver disease. In view of this latter limitation, patients with hepatorenal syndrome and those with reduced renal function who have had or are awaiting liver transplantation should be considered at risk of NSF if they have a GFR below 60 mL/min/1.73 m^2. In children, the Schwartz formula provides a clinically useful estimate of GFR [123].

Step 2: Assess risk–benefit of contrast-enhanced MRI in the patient at risk—A patient at risk of NSF should receive a GBCA only when a risk–benefit assessment for that patient indicates that the benefit clearly outweighs the potential risk or risks. The risk–benefit evaluation should be made by the radiologist in conjunction with the referring physician or physicians and should be properly and prospectively documented. History of previous exposures to GBCAs or of other factors that are thought to act as possible cotriggers of the disease, such as metabolic acidosis, vascular surgery, thrombotic events, and so on, should be taken into account during the risk–benefit assessment of each individual patient. Patients, or parents or guardians in case of minors, should be properly informed of the benefits, risks, and diagnostic alternatives based on all the information available at that time and should provide their consent in writing.

Step 3: Perform any unenhanced MRI sequence that may be helpful before injecting the contrast agent—In the United States, the U.S. Food and Drug Administration (FDA) has requested the prescribing information of all GBCAs to be revised by adding a boxed warning, according to which the use of GBCAs in at-risk patients should be avoided unless the diagnostic information is essential and not available with unenhanced MRI. Therefore, the MR examination should be properly monitored. All unenhanced MRI sequences that may be helpful to make a diagnosis should be performed and the images should be evaluated by an experienced radiologist to ensure that the administration of a GBCA is still deemed necessary.

Step 4: Do not expose at-risk patients to high doses of GBCA—If the use of a GBCA is still deemed necessary after unenhanced MRI, use the lowest dose needed to reliably provide the diagnostic information being clinically sought. According to the boxed warning required by the FDA, the recommended doses should never be exceeded. However, the recommended doses for some agents could be up to 0.3 mmol/kg of body weight. It is recommended to not exceed the standard dose of 0.1 mmol/kg even if the GBCA to be used is approved for higher doses. The use of lower doses, when possible, is encouraged.

Because the risk of NSF is higher when patients are exposed to multiple exposures of a single GBCA dose or to high GBCA doses in a relatively short period of time, the boxed warning recommends that a sufficient period of time be allowed for elimination of the agent from the body before any additional doses are administered. There is no evidence about how long that period of time should be. Because gadolinium has been found in the skin of patients with impaired renal function up to 11 months after the administration of gadodiamide [35, 41], it may be prudent to keep an interval of at least 1 year between administrations of any GBCA to at-risk patients. It is also important to properly track and document any GBCA dose given to patients at risk of NSF for future reference.

Which Agent Should Be Used?

In Europe and Japan, some GBCAs (gadodiamide, Omniscan; gadopentetate dimeglumine, Magnevist; gadoversetamide, OptiMARK) are contraindicated for use in patients at risk of NSF [124–126]. Other GBCAs may be given to at-risk patients, but only if regarded clinically essential. The FDA did not mandate any specific contraindication, but requested that the same boxed warning be added to the prescribing information of all five GBCAs sold in the United States (the three above plus gadobenate dimeglumine [MultiHance, Bracco] and gadoteridol [ProHance, Bracco]) [127]. Therefore, in the United States, the use of any of those five GBCAs should be avoided in patients at risk of NSF unless the diagnostic information is essential and is not available with unenhanced MRI or other imaging modalities.

What To Do After the MRI Examination?

The usefulness of hemodialysis in the prevention of NSF is unknown. However, to enhance and speed up the GBCA elimination, it is recommended that patients on hemodialysis undergo a hemodialysis session no later than 2 hours after the administration of the GBCA. A second hemodialysis session should be considered within 24 hours of the first session [33].

Patients at risk of NSF should be followed up for 1 year after a contrast-enhanced MRI examination to identify any symptom or sign suggestive of NSF and confirm or rule out a diagnosis of NSF. If a new diagnosis of NSF is made, it is recommended that all the regulatory authorities in the United States, Canada, Europe, Asia, and other countries be immediately notified.

Recently, a case has been reported of a 47-year-old man who underwent liver transplantation for cirrhosis secondary to hepatitis C and alcoholism [76]. This case was complicated by primary donor liver dysfunction and acute renal failure requiring dialysis. MR cholangiopancreatography was performed 2 weeks after transplantation with the use of gadodiamide, and a second successful liver transplantation was performed 1 week later. Shortly after this second transplantation, the patient developed biopsy-proven, rapidly progressive NSF that left him wheelchair-bound. After improvement in renal function and various treatments, his plaques softened, fibrosis slowed, and mobility partially improved. The patient underwent a second gadodiamide-enhanced MR cholangiopancreatography examination and, 6 weeks later, further progression of NSF occurred despite normal renal function [76]. Therefore, it is recommended that patients with NSF should never be reexposed to a GBCA even if their renal function goes back to normal over time.

NSF: Final Thoughts

It is unclear if GBCAs can trigger NSF. Nevertheless, it is appropriate to assume for

now that a potential association might exist for all GBCAs. The use of the preventive measures discussed earlier may minimize the risk of developing NSF, as recently reported by investigators at the University of Wisconsin [128].

Summary

To prevent incidents and accidents, it is vital to be cognizant of basic information as well as the latest findings that impact the use of MRI to ensure safety for patients, staff members, and others. This is particularly important because of the evolutionary advancements in MRI technology and the increased potential for hazardous situations to occur in this environment.

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APPENDIX 1: Suggested Diagnostic Criteria to Make a Diagnosis of Nephrogenic Systemic Fibrosis (NSF)

Advanced Renal Failure
- Chronic kidney disease and glomerular filtration rate < 30 mL/min/1.73 m^2
- Acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period

Skin Lesions
- Lesion distribution: mostly upper and lower extremities with involvement of trunk in a minority of cases. Face is involved in approximately 3% of cases
- Lesion morphology: fixed plaques (polygonal, reticular, or amoeboid; red to violaceous to hyperpigmented); induration (unpinchable, firm skin over the extremities with a wooden consistency to palpation and a pattern of bumpiness over the upper arms or thighs); papules, nodules, erythema, and swelling may be also present

Other Signs and Symptoms
- Joint contractures (with reduced range of motion of fingers, wrists, elbows, ankles, and knees)
- Pain (most NSF cases)
- Itching
- Burning sensation
- Paresthesia
- White-yellow scleral plaques with dilated capillary loops (patients < 45 years old)

Dermopathologic Findings
- Increased cellularity (spindled, epithelioid, or both) with few other inflammatory cells
- Increased number of fibrocytes (procollagen I- and CD34-positive by dual immunohistochemical staining)
- Prominent dermal collagen bundles with clefting
- Elastic fibers preserved
- Markedly widened and collagenized subcutaneous septa
- Myxoid substance staining with typical mucin stains

FOR YOUR INFORMATION

The reader's attention is directed to part 2 accompanying this article, titled "MRI Safety Update 2008: Part 2, Screening Patients for MRI," which begins on page 1140.

FOR YOUR INFORMATION

The reader's attention is directed to the commentary on this article, which appears on the following pages.