# Case in Point

# Nephrogenic Systemic Fibrosis

Myrna Muñiz-Ortega, MD and Carlos Rosado, MD

The patient in this case was exposed to a painful, potentially fatal, condition that results in skin thickening and other debilitating symptoms when he underwent contrast MRI. With more and more of these procedures being performed in the United States every year, clinicians must be aware of the possible dangers in this patient population.

Nephrogenic systemic fibrosis (NSF), formerly referred to as nephrogenic fibrosing dermopathy, is a systemic disorder that affects patients with chronic kidney disease. It is characterized by progressive fibrosis and thickening of skin and connective tissues and may involve multiple organs, resulting in significant morbidity. Although the cause of the disorder is still considered under investigation, recent publications have indicated that exposure to gadolinium-based magnetic resonance imaging (MRI) may trigger NSF.[1]

Here, we present the case of an older man with chronic kidney disease who presented with signs of NSF but wasn't diagnosed with the condition until he experienced continued problems. This case highlights the potential danger of performing gadolinium-based MRI in patients with renal dysfunction.

## INITIAL EXAM

An 84-year-old man with stage 3 chronic kidney disease presented to the emergency department (ED) of a VA medical center with significant pruritus and symmetrical erythematous plaques over his lower abdomen and thighs. He reported that his symptoms had been progressing in severity over a two-week period. He was also experiencing weakness in his lower extremities and poor ambulation. A diagnosis of irritant dermatitis secondary to urinary incontinence initially was considered, and he was treated with local care and topical corticosteroids.

A week later, he returned to the ED with worsening of the lesions and more extensive distribution. Some of the lesions showed a peau d'orange appearance with hyperpigmentation and skin thickening (Figure 1). He reported no constitutional symptoms.

This time, a more in-depth history was sought and revealed that, five weeks prior to the initiation of signs and symptoms, an abdomino-pelvic MRI with gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals, Berlin-Wedding, Germany) had been performed to characterize a right renal lesion observed on computed tomography scan. The possibility of NSF was entertained due to gadolinium exposure, and punch biopsies were performed. Histopathologic testing showed keratinizing, slightly atrophic stratified squamous epithelium; dermal spindle cell proliferation with extension to the subcutaneous tissue; and bands of fibrosis, all of which were signs consistent with NSF (Figure 2).

## TREATMENT COURSE

Supportive management was provided to the patient. Approximately six months after the diagnosis he became bedridden, which was considered mostly secondary to the NSF. Around this time, the patient began showing signs of heart disease and was diagnosed with congestive heart failure. He then experienced significant clinical deterioration, mostly from worsening heart failure, and died 10 months later.

## ABOUT THE CONDITION

### The brief history of NSF

NSF, initially coined nephrogenic fibrosing dermopathy, was first observed in 1997 by a dermatopathologist, Philip LeBoit, MD (and was first described in the medical literature in 2000[2]), after he reviewed slides of skin biopsies of patients undergoing unexplained skin thickening.[2] It initially was considered to be a sclero-myxedema-like disorder.[2,3] No gender predilection was noted and age at onset was variable. The common factor found in patients with the condition was the presence of some degree of renal insufficiency, with the majority undergoing hemodialysis.

More recently, Bucala postulated that the state of vascular and endothelial dysfunction present in patients with renal disease contributes to the fibrosing process, with pathogenesis

**Dr. Muñiz-Ortega** is a nephrology fellow and **Dr. Rosado** is the chief of the dialysis unit, both at the VA Caribbean Healthcare System, San Juan, PR. In addition, Dr. Rosado is an assistant professor of medicine at the University of Puerto Rico, San Juan.

mediated by cells named "circulating fibrocytes."[4] These cells participate in normal wound healing and express two markers, CD34 and procollagen I. According to Bucala, the circulating fibrocytes migrate from the circulation to the skin, where they resemble normal fibroblasts.[4]

Initial implicating factors suspected in the development of NSF in patients with renal failure included the presence of vascular interventions (such as fistula procedures and dialysis catheter placement),[2,3] erythropoietin administration,[5] and the presence of serum antiphospholipid antibodies.[6] In 2006, however, a direct link to gadolinium exposure was made by Grobner based on his examination of biopsy specimens obtained from nine patients with the disorder.[1]

In a 2007 population study performed in 467 patients with end-stage renal disease living in Connecticut, 87 patients received a gadolinium-based contrast agent a total of 123 times.[7] Three of the 87 patients developed NSF within two months, representing a 3.4% absolute risk of developing the disease from gadolinium exposure and a 2.4% risk of developing NSF per radiologic study. There were no cases of NSF development in those patients who were not exposed to gadolinium.[7]

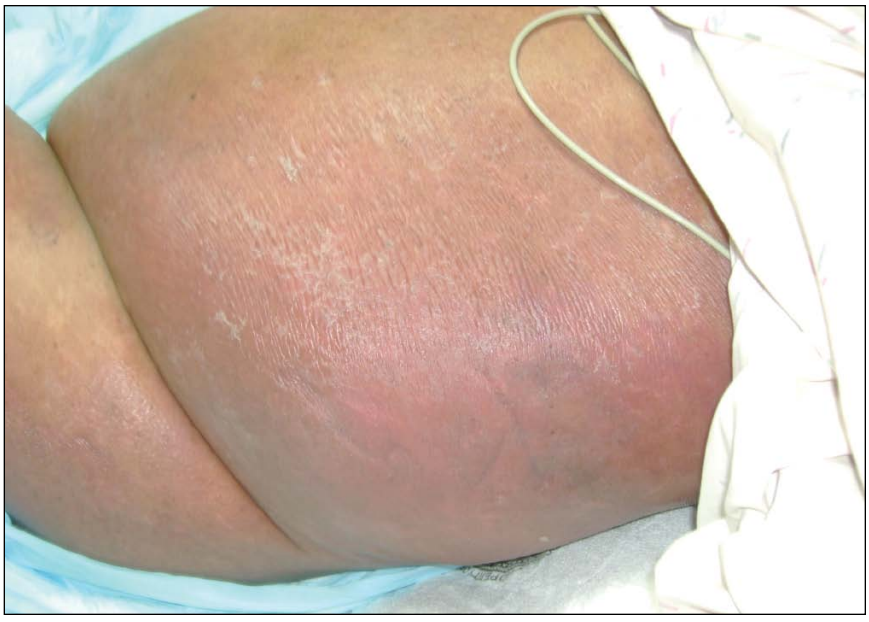

Figure 1. Erythematous plaques over the lower abdomen, with peau d'orange appearance.

## Gadolinium

Gadolinium is a metal. It is part of the lanthanide group and shares chemical and physical characteristics (including size, bonding, coordination, and donor atom preferences) with calcium. Gadolinium has the ability to displace calcium ions, with subsequent binding and activation of the extracellular calcium sensing receptors in many tissues.[8]

The free or the natural form of gadolinium, which is nonchelated, is considered to be toxic and poorly soluble. Exposure to naturally occurring gadolinium is extremely uncommon, as it is a rare earth metal. It is found in commercial ores, monazite, and bastnazite. The industrial uses of gadolinium and its compounds are in the manufacture of magnets, recording devices, and phosphors for color television tubes.[9] Material safety data sheets for gadolinium and its oxide, chloride, boride, and nitrate compounds warn against irritation of skin, mucosae, and respiratory airways and ataxia.[10]

Since gadolinium has seven unpaired electrons, it is highly paramagnetic and serves to enhance the quality of an MRI scan. Gadolinium-based contrast agents used in MRI are manufactured through a chelation process, in which a cyclic or linear chelate forms a stable complex around the metal and allows for 97% of the gadolinium to be eliminated by the kidney. This explains why the half-life is increased in patients with renal insufficiency. In fact, patients with end-stage renal disease might require three or more consecutive sessions of hemodialysis to remove 99% of the amount of gadolinium that would be injected prior to an MRI.[8] Gadolinium is poorly removed by peritoneal dialysis.

Once a gadolinium-based contrast agent enters a patient's circulation, it is susceptible to transmetallation (which is the release of the free gadolinium ions capable of binding to endogenous ions, such as iron, copper, zinc, and calcium).[8] The free gadolinium binds to phosphate (which is elevated in renal disease), producing insoluble particles with tissue deposition.[11] Exogenous iron may serve as a cofactor in the fibrosing process, binding to the gadolinium ligand to produce further oxidant injury. The first signs of NSF can appear anywhere from two to 75 days after exposure to gadolinium.[12]

The deposition of gadolinium in dermal vessel walls of patients with NSF has been detected by electron microscopy and x-ray spectrophotometry. Cutaneous gadolinium in-

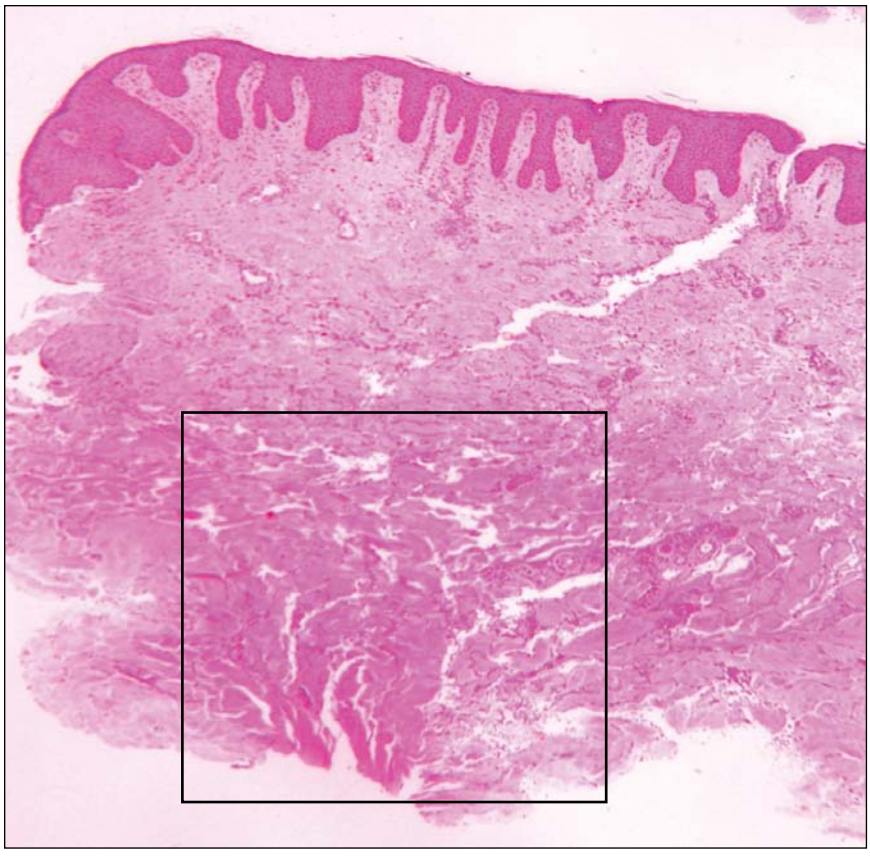

Figure 2. Full thickness skin biopsy showing dermal spindle cells proliferation with extension to the subcutaneous tissue and bands of fibrosis (box).

teracts with circulating fibrocytes to generate the fibrosing cascade.[13]

An FDA advisory was issued in 2006 to warn about the use of gadolinium-based contrast agents in patients with renal insufficiency.[14] A boxed warning is now required for all five gadolinium-based contrast agents that have been approved by the FDA for use in the United States. In addition to gadopentetate dimeglumine, these include gadodiamide (Omniscan, GE Healthcare, Chalfont St. Giles, United Kingdom), gadoteridol (ProHance, Bracco Diagnostics, Inc., Princeton, NJ), gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Inc., Princeton, NJ), and gadoversetamide (OptiMark, Mallinckrodt, Inc., Hazelwood, MO).

Most of the gadolinium-based contrast agents have chelates with a linear composition. Gadoteridol, however, has a cyclic structure, which the evidence so far has shown is less likely to dissociate than linearly structured chelates. For instance, Kuo has reported that 96% of 259 cases of NSF reported to the FDA's MedWatch database by May 2007 were associated with gadodiamide and gadopentetate dimeglubine.[15] Although these agents are the most frequently used in MRI across the United States, Reilly points out in his study that, of the nine cases of NSF reported to be associated with the use of gadoteridol (according to MedWatch as of October 23, 2007), in only one case was it the only gadolinium agent administered to the patient.[16] And in this one case, the patient was given five doses of the metal in one two-year time span. Furthermore, in his retrospective examination of the medical records of all patients receiving long-term hemodialysis at a VA medical center from 2000 to 2007, Reilly found that none of the 141 patients (who had 198 gadoteridol exposures) developed NSF.[16]

## Presentation, diagnosis, and treatment

As of June 2009, 315 cases of NSF had been reported to the International Nephrogenic Systemic Fibrosis Registry at Yale University.[17] Reported manifestations of the disease vary depending on the stage. Early manifestations are characterized by the presence of erythematous plaques that cover a patient's extremities and torso. These plaques have a peau d'orange appearance that may progress to a woody consistency—hence, the initial name of nephrogenic fibrosing dermopathy. In later stages there is loss of skin elasticity. Subsequent joint contractures and impaired mobility are other features of the disease. Involvement of internal organs—such as fibrosis of skeletal muscles, the diaphragm, renal tubules, and coronary arteries—has been reported. In our patient, the possibility of congestive heart failure presenting secondary to progression of NSF was strongly suspected due to the fact that the patient debuted with heart disease at the time he started exhibiting a bedridden state and physical deconditioning.

Laboratory assays are nonspecific, with indicators of inflammation (such as C-reactive protein levels and the erythrocyte sedimentation rate) at times elevated. A full thickness skin biopsy that shows evidence of fibroblast proliferation into the subcutaneous tissue is required for diagnosis.[18]

Continued on next page

Continued from previous page

Therapeutic modalities utilized to date include steroids, photopheresis, plasmapheresis, immunoglobulin, and sodium thiosulfate, but comparative studies are lacking.[19–22] Improvement of renal function may halt or even reverse the process.[3]

## CONCLUSION

It is estimated that more than 20 million MRI scans are performed annually, with 30% of these using gadolinium-based contrast agents.[23] Until safer paramagnetic modalities are available for MRI in patients with chronic kidney disease, it seems prudent for clinicians to: (1) choose noncontrast imaging methods when feasible, (2) weigh the benefits and risks of radiocontrast nephrotoxicity versus NSF in the choice of contrast imaging, (3) actively remove gadolinium by repeated hemodialysis in such patients, and (4) avoid contrast MRI in patients undergoing peritoneal dialysis.

### *Author disclosures*

*The authors report no actual or potential conflicts of interest with regard to this article.*

### *Disclaimer*

*The opinions expressed herein are those of the authors and do not necessarily reflect those of* Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

## REFERENCES


1. Grobner T. Gadolinium—A specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis [published correction appears in *Nephrol Dial Transplant*. 21(6):1745.]? *Nephrol Dial Transplant*. 2006;21(4):1104–1108.
2. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet*. 2000;356(9234):1000–1001.
3. Cowper SE, Su LD, Bhawan J, Robin HS, LeBoit PE. Nephrogenic fibrosing dermopathy. *Am J Dermatopathol*. 2001;23(5):383–393.
4. Bucala R. Fibrocytes: Discovery of a circulating connective tissue cell progenitor. In: Bucala R, ed. *Fibrocytes: New Insights into Tissue Repair and Systemic Fibroses*. Hackensack, NJ: World Scientific; 2007:1–8.
5. Swaminathan S, Ahmed I, McCarthy JT, et al. Nephrogenic fibrosing dermopathy and high-dose erythropoietin therapy. *Ann Intern Med*. 2006;145(3):234–235.
6. Mackay-Wiggan JM, Cohen DJ, Hardy MA, Knobler EH, Grossman ME. Nephrogenic fibrosing dermopathy (scleromyxedema-like illness of renal disease). *J Am Acad Dermatol*. 2003;48(1):55–60.
7. Deo A, Fogel M, Cowper SE. Nephrogenic systemic fibrosis: A population study examining the relationship of disease development to gadolinium exposure. *Clin J Am Soc Nephrol*. 2007;2(2):264–267.
8. Grobner T, Prischl FC. Gadolinium and nephrogenic systemic fibrosis. *Kidney Int*. 2007;72(3):260–264.
9. Periodic table of elements page. Environmental Chemistry.com web site. http://www.environmentalchemistry.com/yogi/periodic/Gd.html. Accessed August 25, 2009.
10. Material safety data sheet page. Electronic Space Products International web site. http://www.espirareearth.com/MSDS/Gadolinium.htm. January 2006. Accessed August 25, 2009.
11. Swaminathan S, Shah SV. New insights into nephrogenic systemic fibrosis. *J Am Soc Nephrol*. 2007;18(10):2636–2643.
12. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: Suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006;17(9):2359–2362.
13. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. *J Am Acad Dermatol*. 2007;56(1):27–30.
14. US Food and Drug Administration. *Information for Healthcare Professionals: Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging (marketed as Magnevist, MultiHance, Omniscan, OptiMARK, ProHance)*. Rockville, MD: US Food and Drug Administration; May 23, 2007. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142884.htm. Updated August 13, 2009. Accessed August 27, 2009.
15. Kuo PH. Gadolinium-containing MRI contrast agents: Important variations on a theme for NSF. *J Am Coll Radiol*. 2008;5(1):29–35.
16. Reilly RF. Risk for nephrogenic systemic fibrosis with gadoteridol (ProHance) in patients who are on long-term dialysis. *Clin J Am Soc Nephrol*. 2008;3(3):747–751. doi:10.2215/CJN.05721207.
17. Cowper SE. Nephrogenic fibrosing dermopathy. NFD/NSF web site. http://www.icnfdr.org. Updated June 18, 2009. Accessed August 25, 2009.
18. Mendoza FA, Artlett CM, Sandorfi N, Latinis K, Piera-Velazquez S, Jimenez SA. Description of 12 cases of nephrogenic fibrosing dermopathy and review of the literature. *Semin Arthritis Rheum*. 2006;35(4):238–249.
19. Gilliet M, Cozzio A, Burg G, Nestle FO. Successful treatment of three cases of nephrogenic fibrosing dermopathy with extracorporeal photopheresis. *Br J Dermatol*. 2005;152(3):531–536.
20. Baron PW, Cantos K, Hillebrand DJ, et al. Nephrogenic fibrosing dermopathy after liver transplantation successfully treated with plasmapheresis. *Am J Dermatopathol*. 2003;25(3):204–209.
21. Chung HJ, Chung KY. Nephrogenic fibrosing dermopathy: Response to high-dose intravenous immunoglobulin. *Br J Dermatol*. 2004;150(3):596–597.
22. Yerram P, Saab G, Karuparthi PR, Hayden MR, Khanna R. 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. *Clin J Am Soc Nephrol*. 2007;2(2):258–263.
23. Idée JM, Port M, Raynal I, Schaefer M, Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: A review [published correction appears in *Fundam Clin Pharmacol*. 2007;21(3):335]. *Fundam Clin Pharmacol*. 2006;20(6):563–576.