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Cardiac and vascular metal deposition with high mortality in nephrogenic systemic fibrosis

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Nephrogenic systemic fibrosis is a severe disabling disease that can follow gadolinium-based contrast exposure. In this study we analyzed the clinical and laboratory records of patients with nephrogenic systemic fibrosis who had a history of exposure to gadolinium-based contrast media and identified their cardiac and vascular events. At autopsy, we found that the heart, blood vessels, and skin of three patients who died of cardiac and/or vascular complications had appreciable amounts of gadolinium, iron, and aluminum as measured by inductively coupled plasma-mass spectrometry and confirmed by x-ray fluorescence. Of the 32 patients with nephrogenic systemic fibrosis studied, 10 died at a median of 112 days after diagnosis. Cardiovascular events contributed to the mortality of 9 patients and included congestive heart failure, recurrent arrhythmias, hypotension, stroke, limb ischemia, posterior ischemic optic neuropathy and sudden death. Our results show that increased cardiac and vascular complications along with short survival in nephrogenic systemic fibrosis are associated with metal accumulation in the heart, blood vessels, and skin of these patients.

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Nephrogenic systemic fibrosis (NSF) is a systemic illness comprised of fibrosis[1] and systemic inflammation,[2,3] and is reported almost exclusively in patients with renal insufficiency who are exposed to gadolinium-based contrast material.[4] On the basis of the demonstration of gadolinium in the skin of NSF patients,[5] the USFDA recently issued a black box warning about the risk of NSF upon gadolinium-based contrast material exposure. Demonstration of significant quantities of insoluble gadolinium in the skin of NSF patients, months after gadolinium-based contrast material exposure and after extensive tissue processing, suggests that gadolinium might have undergone transmetallation *in vivo*. Supporting the importance of transmetallation, all NSF cases reported thus far have been associated with linear magnetic resonance contrast agents[4,6–8] that have inferior thermodynamic stability[9,10] and a kinetic or conditional stability that favors transmetallation.

Only limited data exist on the clinical course and prognosis in NSF.[2,6] Gadolinium-based contrast material exposure induces pro-inflammatory effects and iron mobilization.[6] Iron mobilization, in addition to being an indicator of transmetallation, may increase the risk of cardiovascular complications.[11–13] To study this hypothesis further, in the present study we evaluated the clinical history of all NSF patients who died at a single tertiary-care institution, the University of Arkansas for Medical Sciences (UAMS). In three patients for whom an autopsy was obtained, we quantified metals including gadolinium, iron, and aluminum found in various organs sampled including the heart as well as the arteries.

RESULTS

Demographic and clinical data

The median time of follow-up after NSF diagnosis was 226 (2–1050) days. During this period, there were 10 (31.3%) deaths of the 32 patients followed at UAMS. The median time between gadolinium exposure and NSF diagnosis was 83.5 (4–555) days. The median time between NSF diagnosis and death was 112 (37–263) days. The median age at death was 55

(37–84) years; of those, seven were female. Six patients had diabetes mellitus prior to the diagnosis of NSF, whereas one patient subsequently developed new-onset diabetes mellitus. None of the patients had been treated with aluminum-based phosphate binders. All patients had been exposed to gadodiamide at variable doses (15 ml to angiographic doses) and frequency before the development of NSF. Seven patients had end-stage renal disease at the time of gadolinium exposure and three patients developed acute worsening of kidney function and became dialysis dependent after gadolinium exposure.

Clinical conditions associated with death

Cardiovascular disease contributed to mortality in the majority of UAMS patients ($n=9$) and in one patient at the University of Colorado Health Sciences Center (UCHSC). Sepsis ($n=5$) and discontinuation of dialysis ($n=1$) contributed to mortality in some patients. Cardiac and vascular causes that contributed to the demise of NSF patients include congestive heart failure (CHF; $n=3$), hypotension ($n=4$), cardiac arrhythmias ($n=2$), myocardial ischemia ($n=1$), sudden death ($n=1$), stroke ($n=1$), and limb ischemia ($n=1$). One patient developed blindness secondary to posterior ischemic optic neuropathy. The patient from UCHSC also died of CHF and a persistent cardiac arrhythmia (Table 1). Dialysis was discontinued prior to death in one patient because of multiple comorbidities related to restricted mobility, pain, and an ensuing poor quality of life.

Histopathology data and quantification of metals on an autopsy specimen

A complete autopsy was performed on two NSF patients who died at UAMS. The first patient developed NSF four days after gadolinium exposure and died one month later with new-onset limb ischemia and gangrene, myocardial ischemia, and hypotension (Figure 1). A histopathologic examination of tissues sampled at autopsy demonstrated diffuse ulcerative calcific atherosclerosis, patchy myocardial necrosis and fibrosis, central venous congestion of the liver, calciphylaxis, and necrotic skin upon the lower extremity. On quantitative analysis, significant quantities of gadolinium could be detected in the skin ($411\,\mu g\,g^{-1}$), heart ($344.4\,\mu g\,g^{-1}$), aorta ($48.9\,\mu g\,g^{-1}$), kidney ($190\,\mu g\,g^{-1}$), lungs ($81\,\mu g\,g^{-1}$), liver ($116\,\mu g\,g^{-1}$), and spleen ($53\,\mu g\,g^{-1}$). Analysis of the heart revealed $207\,\mu g\,g^{-1}$ of iron and analysis of the aorta revealed $354\,\mu g\,g^{-1}$ of iron and ($51.9\,\mu g\,g^{-1}$) aluminum.

In the second patient, NSF was diagnosed two months after exposure to gadolinium contrast; this patient died nine months later following sudden onset monocular blindness (posterior ischemic optic neuropathy), stroke, and hypotension. A histopathologic examination of tissues sampled at autopsy revealed diffuse mural calcification of arterial vasculature including the temporal artery and branches to multiple viscera, extensive scleral calcification, diffuse myocardial fibrosis, and central venous congestion of the liver. On quantitative analysis, significant quantities of gadolinium could be detected in the skin ($255\,\mu g\,g^{-1}$), heart ($374\,\mu g\,g^{-1}$), aorta ($436\,\mu g\,g^{-1}$), kidney ($395\,\mu g\,g^{-1}$), lungs ($368\,\mu g\,g^{-1}$), liver ($108\,\mu g\,g^{-1}$), spleen ($277\,\mu g\,g^{-1}$), eyes ($83\,\mu g\,g^{-1}$), and temporal artery ($203\,\mu g\,g^{-1}$). An analysis of the heart revealed increased quantities of iron ($62.9\,\mu g\,g^{-1}$) and aluminum ($29.9\,\mu g\,g^{-1}$). An immunohistochemical stain of a coronary artery showed proliferation of CD34-positive spindle cells; the same artery also contained a significant quantity of gadolinium and iron (Figure 2).

Similarly, in the patient who died of CHF and recurrent arrhythmia at UCHSC, significant quantities of gadolinium could be detected in his heart (two sample areas; 442 and $426\,\mu g\,g^{-1}$) and soft tissue (skin and underlying muscle of the right arm; $100.4\,\mu g\,g^{-1}$). A histopathology of the heart revealed significant fibrosis (Figure 3).

These data were then compared with data from three control skin biopsies obtained during re-excision of basal cell skin cancer and three renal arteries obtained from deceased potential kidney donors for metal content using inductively coupled plasma–mass spectrometry (ICP–MS) (Table 2). As

Table 1 | Demographics and clinical conditions that contributed to mortality in NSF patients

Patient no.	Age (years)	Sex	Diabetes	Dialysis	MRI indication	Dosage/ frequency of gadolinium	Clinical conditions
1	68	M	DM	Yes[a]	Angiogram	40	Hypotension, dialysis withdrawal
2	37	F	DM	Yes[a]	Angiogram	60	Staphylococcal sepsis
3	55	M	No	Yes	MRI brain	Multiple	CHF, sepsis
4	42	F	New DM	Yes	MRI spine	Multiple	Sudden visual loss and stroke, hypotension
5	55	F	DM	Yes[a]	MRI brain	20	CHF, respiratory failure, arrhythmia, sepsis
6	63	M	DM	Yes	Angiogram	100	CHF, hypotension
7	84	F	No	Yes	Angiogram	100	Recurrent atrial fibrillation, staphylococcal sepsis
8	47	F	No	Yes	Angiogram	Angiographic dose	Limb ischemia, hypotension, myocardial ischemia, shock
9	55	F	DM	Yes	MRI leg	20	Sudden death
10	51	F	DM	Yes[a]	MRI brain	Multiple	Sudden cardiac death, hypotension, respiratory failure, sepsis

CHF, congestive heart failure; DM, diabetes mellitus; F, female; M, male; MRI, magnetic resonance imaging; NSF, nephrogenic systemic fibrosis.
[a]Acute renal failure.

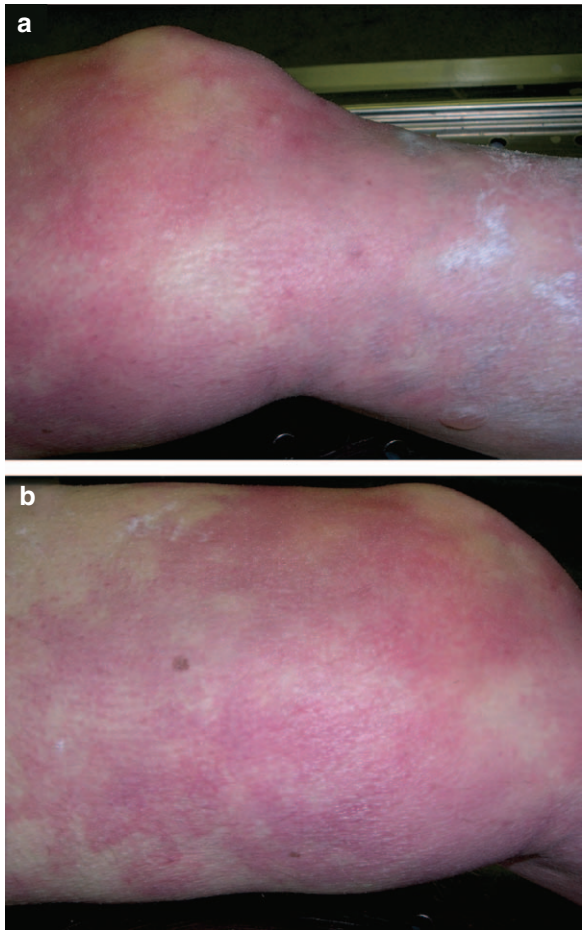

Figure 1 | Nephrogenic systemic fibrosis and limb ischemia after magnetic resonance angiography. New-onset limb ischemia (**a**) and nephrogenic systemic fibrosis (**b**) 1 month after exposure to gadolinium contrast media in a patient with end-stage renal disease on peritoneal dialysis. A significant amount of gadolinium (49 $\mu g\,g^{-1}$) was detected in the aorta 36 days after gadolinium-based contrast exposure.

shown, significantly higher iron accumulation was evident in the NSF biopsies compared with controls. Although statistically insignificant, aluminum content was also higher in the NSF skin biopsies and aorta than in controls. The vascular iron content in the blood vessels of NSF patients was also higher than the reported iron content (9.4 $\mu g\,g^{-1}$) in normal blood vessels.[14]

Because prior reports of gadolinium deposition in the affected tissue of NSF were confined only to the skin and soft tissue, an independent means to confirm gadolinium deposition within cardiac tissue was sought. Sections of fibrotic heart tissue from the UCHSC autopsy case (same sections identified in Figure 3) were cut using a cleaned microtome with new blade onto a pure quartz microscopy slide. This slide was placed in an X-ray fluorescence microprobe that allowed for detection of gadolinium with a sensitivity of about $<1\,\mu g\,g^{-1}$.[15] The tissue demonstrated a strong gadolinium emissions spectra (Figure 4), providing independent verification of gadolinium deposition within the fibrotic cardiac tissue of this patient with NSF.

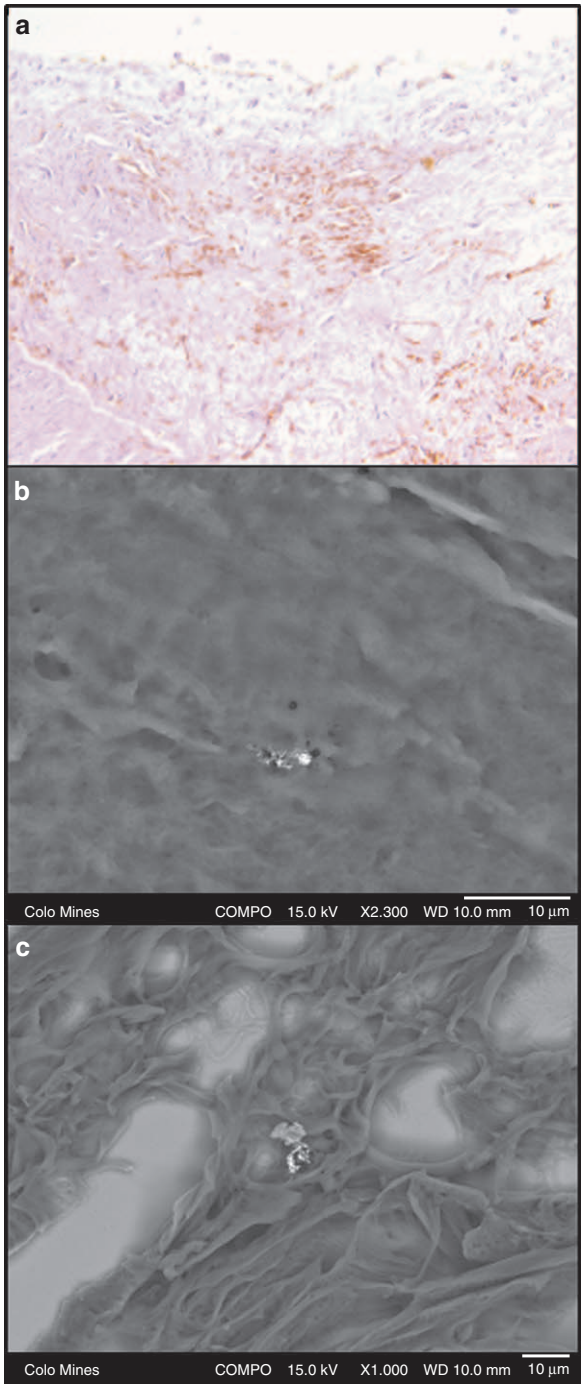

Figure 2 | Coronary artery disease with vascular gadolinium deposition. (**a**) Coronary artery disease in a patient with nephrogenic systemic fibrosis with CD34-positive cells. Appreciable quantities of gadolinium were present in the vessel wall. (**b** and **c**) Iron particles demonstrated in the vessel wall using electron scanning microscopy.

DISCUSSION

In this study, we present several novel observations. First, our data, with a median time to death of just 112 days, indicates that the onset of NSF may be a harbinger of short survival. Second, we report several unique cardiac and vascular events in NSF including sudden monocular blindness secondary to

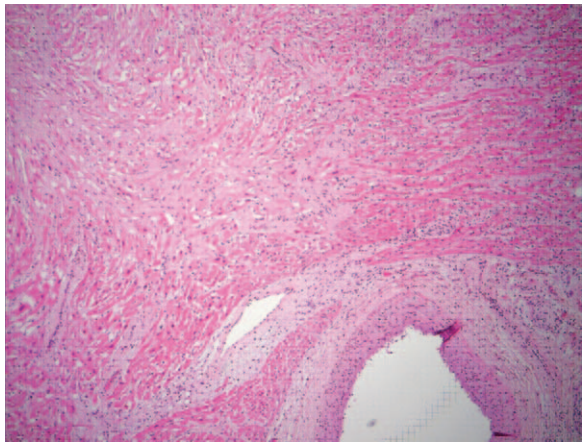

Figure 3 | Myocardial fibrosis in a patient with nephrogenic systemic fibrosis and recurrent cardiac arrythmias. Appreciable quantities of gadolinium (442 μg g^{-1}) were present in the myocardial tissues.

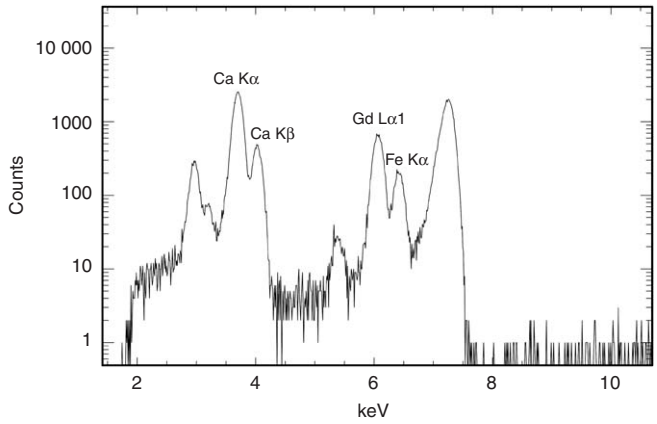

Figure 4 | X-ray fluorescence microprobe for detection of gadolinium in the myocardium of an NSF patient with myocardial fibrosis shown in Figure 3**.** The tissue demonstrates strong gadolinium emission spectra.

Table 2 | Quantification of metal deposition in different organs of NSF patients and controls using ICP–MS

	Heart			Aorta			Skin		
Patients	Gd	Fe	Al	Gd	Fe	Al	Gd*	Fe*	Al
Patient 1	344	207	23	49	138	112	411	974	1965
Patient 2	374	63	30	436	833	204	41	2072	1668
Patient 3	442	130	61	—	—	—	454	618	120
		—		Arteries			Skin		
Controls	—	—	—	Gd	Fe	Al	Gd	Fe	Al
Control 1	—	—	—	0.007	68	14	0.1	107	82
Control 2	—	—	—	0.006	77	2	0	265	119
Control 3	—	—	—	0.011	29	3	0.4	202	138

Al, aluminum; Fe, iron; Gd, gadolinium; ICP–MS, inductively coupled plasma–mass spectrometry; NSF, nephrogenic systemic fibrosis.
All values are presented as μg per g of dry tissue.
Arteries and skin were obtained from different control patients.
*$P<0.1$ versus controls using Wilcoxon test.

posterior ischemic optic neuropathy, limb ischemia, and recurrent cardiac arrythmias. Third, we present the first evidence that NSF is associated with systemic deposition of metals including gadolinium, iron, and aluminum, with the highest quantity of gadolinium deposited in the heart, blood vessels, and skin.

In a recent study, crude mortality rates were 21.2% for patients undergoing peritoneal dialysis and 24.4% for patients undergoing hemodialysis with a mean follow-up of 876 days.[16] According to the USRDS data, the mortality risk for patients on dialysis is 216 per 1000 patient-years.[17] Compared to these findings, our study indicates that mortality is higher (31.3% at 226 days) after an NSF diagnosis and may also be accelerated (median time to death of just 112 days). Specifically, accelerated cardiac and vascular disease was an important cause of death and some NSF patients died of cardiac and limb ischemia as early as one month after the onset of gadolinium-associated NSF (Figure 1). Additionally, these patients suffered unique vascular events such as posterior ischemic optic neuropathy. Although the mechanism of these excess and unique cardiac and vascular events in NSF is unknown, our data suggest that the accumulation of metals such as gadolinium, iron, and aluminum might account for these events. In fact, the highest levels of gadolinium were found in the heart and aorta in two of our patients with myocardial fibrosis who died with myocardial ischemia and recurrent cardiac arrythmias.

Possible mechanisms for gadolinium toxicity are currently under evaluation. One such postulated mechanism, already reported by us, includes profound iron mobilization, transferrin oversaturation, and a systemic inflammatory response as a result of gadolinium exposure.[18] Iron is capable of inducing transmetallation of gadolinium chelates and this may liberate free gadolinium that is toxic.[9] Iron mobilized by the introduction of gadolinium contrast may also be directly toxic to the endothelium via oxidative stress (Fenton reaction).[12] Finally, aluminum[19–22] and systemic inflammation[12] can aggravate iron-mediated injury. Thus, a combination of free gadolinium, catalytic iron, aluminum, systemic inflammation, and oxidative stress may initiate endothelial injury that evolves into a systemic fibrosing process of the tissues that is characteristic of NSF. Thus, metal deposition may contribute to as well as worsen any preexisting myocardial fibrosis and vascular calcification,[23] ventricular dysfunction, and arrhythmogenicity and high mortality in NSF. Preexisting vascular disease,[3,24] a known risk factor for NSF, may amplify these risks.

Bone aluminum accumulation is a well-known phenomenon in dialysis patients.[25] However, to our knowledge, cutaneous or vascular aluminum accumulation has never been reported. Possible mechanisms and source of excess aluminum accumulation in the tissues of NSF patients is unclear. However, we could speculate several possible mechanisms. Competition for transferrin binding between iron and aluminum could be important.[26] Unavailability of

transferrin-binding sites because of low serum transferrin levels and saturation of the remaining binding sites by mobilized iron[6] and gadolinium[27,28] may result in excess plasma free aluminum and consequent tissue deposition. Increased dietary intake in the context of poor urinary excretion could have contributed additionally to tissue aluminum load.[29] It is feasible that some of the excess tissue aluminum along with iron participated in the transmetallation of gadolinium contrast.

Sepsis and discontinuation of dialysis are two additional factors that contributed to death in NSF-afflicted patients. Although sepsis is a common cause of death in dialysis patients,[30] gadolinium toxicity and deposition may increase the risk of sepsis through iron mobilization,[31] pro-inflammatory/immunomodulatory effects,[6] and deposition in the reticuloendothelial system.[32,33] Our discovery of renal deposition of gadolinium is also an important finding because acute, irreversible renal failure has been observed in some patients who develop NSF after exposure to gadolinium contrast.[6] Iron is well-known to play a role in kidney injury leading to renal tubular toxicity and fibrosis.[34] This finding is of significant relevance even in patients with end-stage renal disease as loss of residual renal function significantly increases the risk of cardiovascular complications and death.[35]

There are several limitations to our study including the retrospective nature of the observations and limited sample size. In addition, controls for metal analysis were obtained from patients who did not have renal insufficiency, were not exposed to gadolinium, and did not have NSF. Thus, we cannot rule out tissue accumulation of metals in patients with renal failure exposed to gadolinium but without NSF. A systemic evaluation of adjusted annual mortality rates in NSF patients could not be evaluated by this study because of a highly variable follow-up and small sample size. We observed higher tissue metal accumulation and concomitant increased cardiovascular mortality in NSF. However, our current study is not designed to address a cause–effect relationship between these two observations. Additional studies will be required to address some of these issues.

On the basis of our observations, we conclude that onset of NSF heralds a high risk of mortality from cardiac and vascular injury and fibrosis potentially related to systemic deposition of gadolinium, iron, and aluminum, demonstrable in various organs but with the highest amount of gadolinium detected in the heart and blood vessels. We speculate that metal deposition may potentially determine the severity of clinical manifestations and outcome of gadolinium contrast toxicity in patients with renal insufficiency. Finally, it is conceivable that in some patients cardiovascular manifestations of NSF may occur with variable or minimal involvement of other organs such as skin.

MATERIALS AND METHODS

Approval from the Institutional Review Board of UAMS and appropriate exemption from the Colorado Multiple Institution Review Board (COMIRB) was obtained. Thirty-four patients with NSF were identified from UAMS records and additional follow-up data could not be obtained in two of these patients. Of the remaining 32 UAMS patients diagnosed with NSF, 10 died and their data are included for further analysis. Relevant clinical history and laboratory parameters were recorded and the factors leading to death were abstracted from their medical records. Cardiovascular complications such as hypotension, arrhythmias, organ ischemic syndromes (stroke, myocardial infarction, and limb ischemia), sudden cardiac death, and CHF after NSF diagnosis were recorded. Sepsis occurring after an NSF diagnosis was also recorded. The date of gadolinium exposure, type of gadolinium contrast agent administered, and estimated renal function at the time of exposure were examined.

In two NSF patients who died at UAMS, a complete autopsy was performed after an informed consent was obtained, and the sampled organs and blood vessels were evaluated for gadolinium, iron, and aluminum quantity using ICP–MS. Autopsy data on one additional NSF patient who died at the University of Colorado Health Sciences Center (UCHSC) were also included.

De-identified paraffin-embedded blocks were submitted to investigators in Colorado for the purpose of gadolinium quantification. Quantitative measurement via ICP–MS on 30 tissue blocks was performed in a fashion similar to the previously published techniques of one of the authors (WAH).[36] Multiple 30 μM sections were cut from tissue blocks and then deparaffinized using twice-distilled xylene and ethanol. Both the autopsy tissues and control tissue biopsies were subjected to a similar de-paraffinization procedure. After drying at 105 °C until a constant dry weight was obtained, samples were placed into quartz tubes and digested with trace-metal-grade strong acids to fully oxidize all organic material. Digested samples were analyzed using ICP–MS on a PerkinElmer 6100 DRC Plus instrument (PerkinElmer Life and Analytical Sciences Inc., Waltham, MA, USA). Total gadolinium (Gd) ions were monitored at dual masses of 157.924 Da for ^{158}Gd and 159.927 Da for ^{160}Gd. Other ions monitored included iron (Fe) at the dual masses of X (^{54}Fe, 53.940 Da) and Y (^{56}Fe, 55.935 Da), and aluminum (Al) at the mass of Z (^{27}Al, 26.982 Da). Determination of micrograms of gadolinium and other metals per milligrams of dry tissue was calculated. Positive and negative control blanks were included in the analysis to confirm proper functioning of the equipment.

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REFERENCES

1. Cowper SE, Robin HS, Steinberg SM *et al.* Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; **356**: 1000–1001.
2. Swaminathan S, Ahmed I, McCarthy JT *et al.* Nephrogenic fibrosing dermopathy and high-dose erythropoietin therapy. *Ann Intern Med* 2006; **145**: 234–235.
3. Sadowski EA, Bennett LK, Chan MR *et al.* Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007; **243**: 148–157.
4. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; **12**: 3604–3605.
5. High WA, Ayers RA, Chandler J *et al.* Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 2007; **56**: 21–26.
6. Swaminathan S, Horn TD, Pellowski D *et al.* Nephrogenic systemic fibrosis, gadolinium, and iron mobilization. *N Engl J Med* 2007; **357**: 720–722.

7. 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**: 2359–2362.
8. Broome DR, Girguis MS, Baron PW *et al.* Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am J Roentgenol* 2007; **188**: 586–592.
9. Idee JM, Port M, Raynal I *et al.* Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundam Clin Pharmacol* 2006; **20**: 563–576.
10. Swaminathan S, Shah SV. New insights into nephrogenic systemic fibrosis. *J Am Soc Nephrol* 2007; **18**: 2636–2643.
11. Yachie A, Niida Y, Wada T *et al.* Oxidative stress causes enhanced endothelial cell injury in human heme oxygenase-1 deficiency. *J Clin Invest* 1999; **103**: 129–135.
12. Shah SV, Alam MG. Role of iron in atherosclerosis. *Am J Kidney Dis* 2003; **41**: S80–S83.
13. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**: 1685–1695.
14. Stadler N, Lindner RA, Davies MJ. Direct detection and quantification of transition metal ions in human atherosclerotic plaques: evidence for the presence of elevated levels of iron and copper. *Arterioscler Thromb Vasc Biol* 2004; **24**: 949–954.
15. Lai B, Vogt S, Maser J *et al.* Applications and future prospects for x-ray fluorescence microprobe analysis. *Microsc Microanal* 2007; **14**: 1426–1427.
16. Jaar BG, Coresh J, Plantinga LC *et al.* Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med* 2005; **143**: 174–183.
17. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. *J Am Soc Nephrol* 2007; **18**: 2644–2648.
18. (CDC) CfDCaP. Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents—St Louis, Missouri, 2002–2006. *MMWR Morb Mortal Wkly Rep* 2007; **56**: 137–141.
19. Kapiotis S, Hermann M, Exner M *et al.* Aluminum ions stimulate the oxidizability of low density lipoprotein by Fe^{2+}: implication in hemodialysis mediated atherogenic LDL modification. *Free Radic Res* 2005; **39**: 1225–1231.
20. Halliwell B. Oxidants and the central nervous system: some fundamental questions. Is oxidant damage relevant to Parkinson's disease, Alzheimer's disease, traumatic injury or stroke? *Acta Neurol Scand Suppl* 1989; **126**: 23–33.
21. Crichton RR, Wilmet S, Legssyer R *et al.* Molecular and cellular mechanisms of iron homeostasis and toxicity in mammalian cells. *J Inorg Biochem* 2002; **91**: 9–18.
22. Becaria A, Campbell A, Bondy SC. Aluminum as a toxicant. *Toxicol Ind Health* 2002; **18**: 309–320.
23. Ishizaka N, Saito K, Mitani H *et al.* Iron overload augments angiotensin II-induced cardiac fibrosis and promotes neointima formation. *Circulation* 2002; **106**: 1840–1846.
24. Swaminathan S, Leung N. Nephrogenic fibrosing dermopathy: lessons from the past. *Int J Dermatol* 2006; **45**: 639–641.
25. Kausz AT, Antonsen JE, Hercz G *et al.* Screening plasma aluminum levels in relation to aluminum bone disease among asymptomatic dialysis patients. *Am J Kidney Dis* 1999; **34**: 688–693.
26. Van Landeghem GF, D'Haese PC, Lamberts LV *et al.* Competition of iron and aluminum for transferrin: the molecular basis for aluminum deposition in iron-overloaded dialysis patients? *Exp Nephrol* 1997; **5**: 239–245.
27. Jackson GE, Wynchank S, Woudenberg M. Gadolinium(III) complex equilibria: the implications for Gd(III) MRI contrast agents. *Magn Reson Med* 1990; **16**: 57–66.
28. Jackson GE, Byrne MJ. Metal ion speciation in blood plasma: gallium-67-citrate and MRI contrast agents. *J Nucl Med* 1996; **37**: 379–386.
29. DeVoto E, Yorkel RA. The biological speciation and toxicokinetics of aluminum. *Environ Health Perspect* 1994; **102**: 940–951.
30. Foley RN, Guo H, Snyder JJ *et al.* Septicemia in the United States dialysis population, 1991–1999. *J Am Soc Nephrol* 2004; **15**: 1038–1045.
31. Zager RA, Johnson AC, Hanson SY. Parenteral iron therapy exacerbates experimental sepsis. *Kidney Int* 2004; **65**: 2108–2112.
32. Mizgerd JP, Molina RM, Stearns RC *et al.* Gadolinium induces macrophage apoptosis. *J Leukoc Biol* 1996; **59**: 189–195.
33. Iimuro Y, Yamamoto M, Kohno H *et al.* Blockade of liver macrophages by gadolinium chloride reduces lethality in endotoxemic rats—analysis of mechanisms of lethality in endotoxemia. *J Leukoc Biol* 1994; **55**: 723–728.
34. Shah SV, Baliga R, Rajapurkar M *et al.* Oxidants in chronic kidney disease. *J Am Soc Nephrol* 2007; **18**: 16–28.
35. Termorshuizen F, Dekker FW, van Manen JG *et al.* Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 2004; **15**: 1061–1070.
36. High WA, Ayers RA, Cowper SE. Gadolinium is quantifiable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 2007; **56**: 710–712.