REPORT

Gadolinium deposition in nephrogenic fibrosing dermopathy

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There is growing recognition of the association between the use of gadolinium-containing radiocontrast agents for magnetic resonance imaging and the serious dermal and systemic disease nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF). The pathogenesis of this entity remains unclear; however, our recent observations suggest a likely mechanism for the initial dermal manifestations of this gadolinium toxicity. (J Am Acad Dermatol 10.1016/j.jaad.2006.10.048.)

In 2000, Cowper et al[1] reported a series of 14 hemodialysis patients with thickening and hardening of the skin and scleromyxedema-like features. None of the patients, however, demonstrated a monoclonal gammopathy. Clinically, the lesions presented as hyperpigmented patches and plaques on the extremities. The following year, the same group of investigators described in greater detail the pathologic changes associated with this disease and termed the condition nephrogenic fibrosing dermopathy (NFD).[2] Systemic involvement has been subsequently reported, leading to the suggestion that this entity be called nephrogenic systemic fibrosis.[3] As NFD appeared to be a recently occurring phenomenon, it was postulated that exposure to some insult or new clinical practice may be responsible. Grobner[3] and Marckmann et al[4] described separate case series of patients administered gadolinium (Gd)-containing radiocontrast materials during magnetic resonance imaging (MRI) studies who subsequently developed NFD and proposed that this metal may be responsible for the disease. Until now, the presence of Gd in cutaneous biopsies from patients with NFD has not been reported.

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CASE REPORT

A 68-year-old white female presented to the Vanderbilt University Dermatology Clinic in June 2006 with a 3-week history of thickened skin on her extremities which began as painful soft tissue swellings and rapidly became indurated. Her past history was significant for chronic hepatitis C infection—induced hepatic failure for which she received a liver transplant in 1995. Cyclosporine therapy—induced renal failure necessitated hemodialysis in January 2006. Three weeks later she underwent an in-patient MRI heart scan using Gd-containing contrast material. During this hospitalization she was consistently hypocalcemic, hyperphosphatemic, and acidotic. Her medications included cyclosporine, metoprolol, coumadin, and amiodarone. She has been exposed to no other radiocontrast materials subsequently.

On physical examination, her bilateral arms and forearms, calves, and shins demonstrated woody induration without appreciable color changes. A punch biopsy from the left posterior arm demonstrated diffuse dermal fibroplasia with spindle cells extending into the subcutaneous tissues, mild interstitial mucin deposition, and minimal inflammation, features consistent with NFD. Scanning electron microscopy and energy dispersive x-ray spectroscopy (SEM/EDS) demonstrated Gd detected only in areas of calcium phosphate deposition in blood vessels (Fig 1). [F1-4/C]

The patient is currently undergoing extracorporeal photophoresis for her condition and has experienced modest improvement.

DISCUSSION

NFD is a recently described entity occurring almost exclusively in patients undergoing hemodialysis for end stage renal disease (ESRD); while the instance is rare, patients have developed this condition while performing peritoneal dialysis.[2]

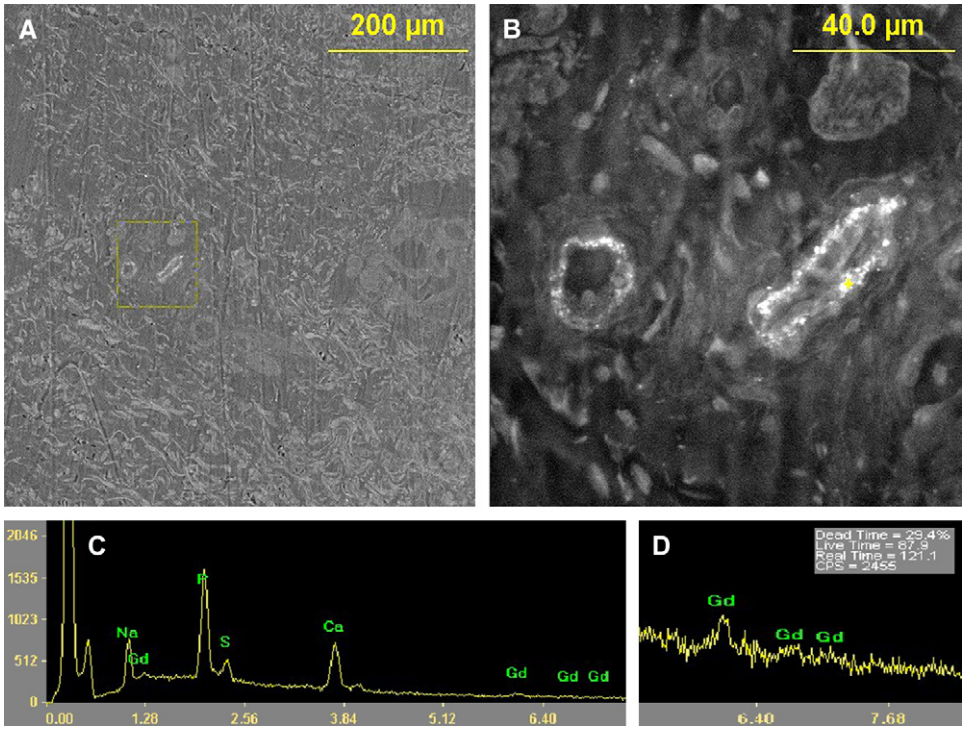

Fig 1. Scanning electron microscopy, backscattered electron images of cut surface of paraffin block of skin biopsy, low magnification (**A**), and detail (**B**), showing dermal vessel wall deposits of calcium, phosphorus, sodium, and gadolinium. Energy dispersive x-ray spectra show major composition of bright areas is sodium-calcium-phosphate (**C**), with gadolinium detected at much lower concentrations (**D**).

Beginning as swelling of the hands and feet, the skin becomes progressively thickened with a peau d'orange appearance.[5] This progression appears to proceed at a variable rate, with some patients describing rapid advancement of the indurated areas while others note a much slower course. Most patients describe the lesions as painful or pruritic and significantly debilitating. Involvement of the trunk and buttocks may ensue, but the head and neck are rarely affected. The skin hardening resembles scleroderma or morphea with joint contractures, sclerodactyly, and limitation of motion ultimately occurring in most patients.[2,5] Systemic involvement of the lungs, myocardium, striated muscles, and diaphragm have also been reported.[6] No specific laboratory findings have been described, although C reactive protein and erythrocyte sedimentation rate are often elevated.[5] Importantly, monoclonal gammopathies have not been reported.

The histologic features of cutaneous biopsies vary depending on the age of the lesion. When biopsied early in the disease, the changes may be subtle, with only a scant proliferation of spindled fibroblasts and minimal evidence of collagen production appreciated. Older lesions, however, demonstrate more florid numbers of fibroblasts and collagen deposition in the reticular dermis and subcutis.[2,6] The subcutaneous septae may be expanded by this fibrotic process. Mildly increased amounts of stromal mucin may also be noted but inflammation is typically absent. $CD34^+$ dermal dendrocytes are abundant, and factor $XIIIa^+$ and $CD68^+$ monocytes and multinucleated cells are found in increased numbers. Mendoza et al[5] have also noted increased numbers of these cells in early lesions.

The patient with fatal NFD and systemic involvement reported by Ting et al[6] demonstrated similar findings in the skin as well as "large zones of calcium deposition within the collagen bundles without vessel calcification." At autopsy, the patient's diaphragm and psoas muscle showed significantly increased fibrous tissue with vascular and interstitial calcium deposits. Other internal organs including the heart, lungs, kidneys, and rete testes also demonstrated calcium deposition. Similar findings have been reported by others.[5]

The pathogenesis of this condition is unclear, with coagulation abnormalities, angiotensin-converting enzyme inhibitor administration, recent vascular surgery, or intervention and the presence of antiphospholipid antibodies having been proposed.[3] The early infiltration of the dermis by factor

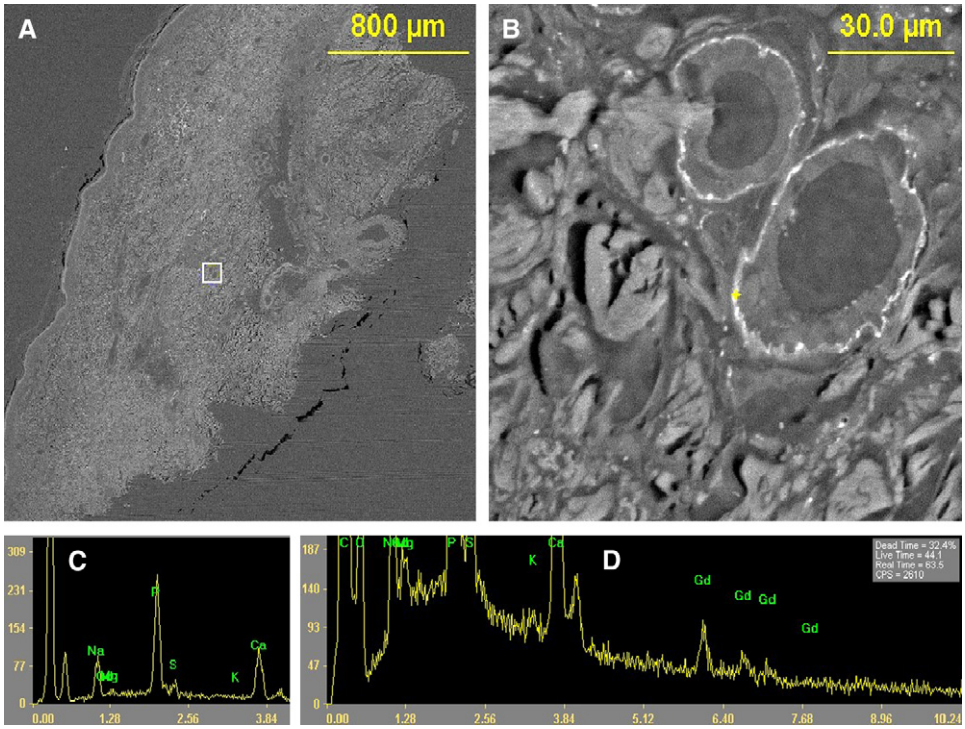

Fig 2. Scanning electron microscopy, backscattered electron images of cut surface of paraffin block of skin biopsy, low magnification (**A**), and detail (**B**), showing deposition of calcium, phosphorus, sodium, and gadolinium along the basal lamina of eccrine sweat glands. Energy dispersive x-ray spectra show major composition of bright areas is sodium-calcium-phosphate (**C**), with gadolinium detected at much lower concentrations (**D**).

Table I. Clinical characteristics of the patients studied

	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)/Sex	68/F	31/F	41/F	46/M
Cause of renal failure	Cyclosporine toxicity	Systemic lupus erythematosus	Insulin-dependent diabetes mellitus	Polycystic kidney disease
Length of time on dialysis	3 weeks	8 months	43 months	14 months
Amount of Gd administered	3.8 gm	5.8 gm	Unknown	Unknown
Time to development of symptoms	5 months	5 months	Unknown	6 months
Serum calcium at time of MRI (normal, 8.5-10.5 mg/dl)	7.2 mg/dl	9.0 mg/dl	Unknown	Unknown
Serum phosphate at time of MRI (normal, 2.5-4.5 mg/dl)	6.6 mg/dl	5.2 mg/dl	Unknown	Unknown
Acidosis	Yes	No	Unknown	Unknown
Treatment	ECP	Retransplanted	ECP	ECP
Current status	Alive	Alive	Alive	Deceased

ECP, Extracorporeal photophoresis; *Gd*, gadodiamide; *MRI*, magnetic resonance imaging.

XIIIa$^+$/CD68$^+$ cells may represent a host response to noxious stimuli.[5] In situ hybridization studies of affected skin, muscle, and fascia have demonstrated increased expression of transforming growth factor β1 mRNA.[5] It is possible that these dermal dendrocytes may be responsible for the production of this growth factor and the ensuing fibrosis.

A more attractive hypothesis involves bone marrow–derived cells involved in normal wound repair termed circulating fibrocytes.[7] These cells stain for CD34, CD45RO, and type 1 collagen, are recruited into the skin where they are involved in wound repair and fibrotic processes, and have been described in NFD patient biopsies.[8] Ortonne et al[8]

postulated that "a recently introduced material, possibly a contrast agent, medication, or other allergen" might be deposited in the tissues and serve as a surrogate target for circulating fibrocytes.

Grobner[3] reported 5 patients with ESRD on hemodialysis who developed NFD 2 to 4 weeks after undergoing a Gd-EDTA enhanced MRI scan. He noted that affected patients had been on dialysis longer and were experiencing metabolic acidosis at the time of their scans compared to similarly evaluated patients without NFD. Marckmann et al[4] described 13 patients with ESRD on hemodialysis affected by NFD an average of 25 days following their exposure to Gd, but failed to associate their condition with metabolic acidosis. NFD without prior Gd exposure was not observed and no cases have developed since suspending the use of Gd-containing contrast agents.

Gd-DTPA (gadodiamide) was introduced in 1988 as a paramagnetic contrast agent for use in MRI scans and was believed to be safe for patients with impaired renal function.[3] Free Gd ions can form precipitates with anions, such as phosphate, because of its poor solubility, and it is considered highly toxic in its ionic form.[8] Marckmann et al[4] have posited that NFD may result from liberated Gd ions deposited in the tissues. These molecules are known to be extremely toxic and to produce deposits of Gd with calcium phosphates in the tissues of rodents.[9] The US Food and Drug Administration has recently issued a public health advisory regarding these agents, citing "a possible link between NSF/NFD and exposure to gadolinium-containing contrast agents."[10]

Calcification was not appreciated in tissue sections stained with hematoxylin–eosin or von Kossa (calcium) in our patient, and Gd deposition was restricted to areas with concomitant calcium phosphate deposition in the reported patient as well as in biopsies evaluated from additional patients with NFD (Table I). Gd deposition along eccrine sweat
[F2-4/C] gland basal lamina was also noted in patient 4 (Fig 2). Calcium phosphate deposits are common in cutaneous biopsies taken from patients undergoing hemodialysis, presumably secondary to altered calcium and phosphate metabolism. We believe cutaneous Gd deposition may serve as a nidus for the development of NFD. Gadolinium deposition at sites other than those associated with discernable calcium phosphate deposition cannot be excluded, as only retained, insoluble Gd is detectable in our tissue samples with SEM/EDS methodology. Whether Gd deposition precedes or follows tissue calcification is unknown. Additionally, whether the presence of elevated circulating and/or tissue calcium and phosphate induce release of the (toxic) free Gd from the contrast agent is unclear.

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