Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy: A Primer for Radiologists

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Abstract: Nephrogenic systemic fibrosis (NSF) is a rare, idiopathic systemic fibrosing disorder that is predominantly characterized by a clinicopathologically distinct symmetric dermopathy and debilitating joint contractures. The condition affects patients with renal insufficiency and appears to show improvement with prompt restoration of renal function. Although NSF was initially reported in the United States as nephrogenic fibrosing dermopathy, it has subsequently been described in patients in Europe and Asia. More than 215 cases of NSF have been reported in the nephrogenic fibrosing dermopathy/NSF registry that is currently maintained at the Yale University. Recent reports suggest a possible etiologic link between systemic administration of gadolinium-containing magnetic resonance imaging contrast agents in patients with renal insufficiency and the development of NSF.

Key Words: renal failure, gadolinium, MRI, systemic fibrosis

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NEPHROGENIC SYSTEMIC FIBROSIS/ NEPHROGENIC FIBROSING DERMOPATHY: BACKGROUND

In 2000, Cowper and colleagues[1] described a unique scleromyxedema-like dermopathy that developed in 15 renal dialysis patients seen over a period of 3 years. The first few patients were seen by the nephrologists at a renal transplantation clinic in southern California. The condition which they subsequently named as nephrogenic fibrosing dermopathy (NFD) manifested with marked skin thickening/ hardening and hyperpigmentation of the limbs and the trunk.[2] Flexion contractures of the upper extremity joints were occasionally associated with the condition. Nephrogenic fibrosing dermopathy was rechristened as nephrogenic systemic fibrosis (NSF) owing to the systemic nature of the disorder.[3,4] Since January 2002, 20 of a total of 400 patients in Denmark with severely impaired renal function that received Omniscan (Gadodiamide; GE Healthcare, Princeton, NJ) developed NSF.[5] After a report by the Danish Medicines Agency on May 29, 2006, that linked NSF with administration of gadolinium-based contrast agents for magnetic resonance (MR) angiography procedures (within 3 months of disease onset), the US Food and Drug Administration (FDA) issued a public health advisory on December 22, 2006.[6]

NSF/NFD: WHAT IS IT?

Nephrogenic systemic fibrosis is a recently described, idiopathic systemic fibrosing disorder that occurs in patients with acute or chronic renal failure and commonly manifests as a symmetric, extremity dermopathy of insidious onset.[1,2,7] Nephrogenic systemic fibrosis may rapidly progress to a debilitating illness in many patients due to joint immobility and flexion contractures; wheelchair dependency may occur within a span of few weeks. Intractable pain syndrome has also been described in some patients. Nephrogenic systemic fibrosis contributes to long-term morbidity and occasional mortality.[2,4,8]

NSF/NFD: WHERE AND HOW ARE THE SKIN LESIONS?

The primary skin lesions of NSF/NFD include symmetric, erythematous papules that coalesce to brawny plaques with an "ameboid" or serpiginous edge.[2] The extremities and trunk are the characteristic target sites of the skin lesions. Woody or peau d'orange consistency of the skin is characteristic. Pruritus and burning pain are common symptoms.[2] The initial clinical presentation of NSF may simulate cellulitis with marked extremity swelling and redness. Sparing of the face is a characteristic feature that helps distinguish NSF from scleromyxedema, a rare chronic idiopathic dermopathy that is usually accompanied by a monoclonal paraproteinemia/gammopathy.[1,2]

NSF/NFD: MORE THAN JUST A SKIN DISEASE?

An autopsy study in a 60-year-old man with progressive NFD revealed systemic fibrosis and calcification involving the skeletal muscle, kidney, and rete testis.[3] Subsequent studies have established that NSF is characterized by systemic fibrosis involving skeletal muscle, esophagus, lungs, myocardium, and kidney.[4,9] Most patients develop joint contractures and muscle weakness within days to weeks of onset of the disease that may lead to significant immobility in some patients.[8] Patients with NSF have a higher incidence of chronic pulmonary fibrosis, often idiopathic in nature.[10]

NSF/NFD: WHO GETS IT?

Nephrogenic systemic fibrosis occurs exclusively in patients with preexisting renal insufficiency. Approximately 90% of patients with NSF harbor dialysis-dependent chronic renal insufficiency. Although development of NSF has been

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ascribed to renal dysfunction from a multitude of factors, it is not likely related to the duration or severity of renal disease.[11] Antecedent systemic administration of gadolinium-containing contrast agents, particularly gadodiamide (within 3 months of disease onset) has been increasingly reported in patients with NSF.[12–14]

Although the mean age of occurrence is 46 years, NSF affects patients of all ages. Pediatric patients with NSF have also been described in the literature.[15] There is no known sex predilection.

NSF/NFD: HOW DO PATIENTS GET IT? IS THERE A "TRIGGER" EVENT?

The etiopathogenesis of NSF has not been conclusively established. Why certain patients with renal insufficiency develop the condition is not clearly known at present. Several "trigger" events have been described that include nontransplant-related surgical procedures, hepatorenal syndrome, vessel trauma (including vascular surgeries), use of angiotensin-converting enzyme inhibitors, and use of high-dose gadolinium-containing MR contrast agents.[8,12–14,16] Gadolinium agents have been used in 75 of 215 reviewed cases of NSF.[6] It is hypothesized that vessel injury may trigger inappropriate proliferation and activity of circulating fibrocytes (CFs) leading to deposition of collagen and matrix in the target tissues.

NSF/NFD: WHAT CAUSES FIBROSIS?

Systemic fibrosis, particularly dermal fibrosis, is a hallmark feature of NSF. Circulating fibrocyte, an immunologically unique CD-34 positive cell, has been found to be the predominant cell population in skin biopsy specimens in patients with NSF. Circulating fibrocyte is a bone marrow–derived leukocyte that is postulated to play a major role in wound healing and tissue remodeling. It is hypothesized that NSF results from aberrant traffic and proliferation of CFs in the tissues after a yet-to-be-established "immunological trigger."[8,17] The CFs in the target tissues contribute to marked collagen and matrix deposition.

GADOLINIUM & NSF/NFD: THE "REAL" PARTNER IN CRIME?

Grobner[13] was the first to suggest a causative role for gadolinium-containing contrast agents in the pathogenesis of NSF. Five of 9 end-stage renal disease patients developed NSF 2 to 4 weeks after undergoing MR angiography studies. Gadodiamide was the contrast agent used in all patients (average contrast volume being 35 mL). All affected patients had metabolic acidosis.[13] Subsequent studies have suggested that NSF is temporally related to systemic administration of gadodiamide in patients with moderate to severe renal insufficiency.[12,14,18] Nephrogenic systemic fibrosis developed after a latent period of 2 to 11 weeks; the volume range of gadodiamide used was 9 to 25 mmol (average, 37 mL).[12,14] Antecedent gadodiamide use has been documented in more than 95% of about 100 NSF patients being surveyed.[19] Of the 5 FDA-approved gadolinium agents for MR imaging (MRI) studies, 3 agents have been linked to the development of NSF.[6] Nephrogenic systemic fibrosis has been associated with both standard-dose and high-dose gadolinium administration. The exact role of gadolinium chelates in the etiopathogenesis of NSF is still being investigated.

GADOLINIUM IN TARGET SITES OF NSF/NFD: REAL CULPRIT OR AN INNOCENT BYSTANDER?

Intracellular gadolinium has been recently identified in skin biopsy specimens by using electron microscopy and x-ray spectroscopy.[16,20] Gadolinium deposits were documented in areas of calcium phosphate deposition in dermal blood vessels.[16] High et al[20] identified gadolinium in 4 of 13 skin and soft tissue specimens from 7 NSF patients. Tissue deposition of intracellular, toxic, free gadolinium ions may lead to inflammatory reaction with recruitment and increased activity of CFs ultimately resulting in tissue fibrosis.[20] Alternatively, the excess chelate present in certain gadolinium agents may alter metal homeostasis within the tissues. Interestingly, High et al[20] found high concentrations of other metals such as zinc, copper, and iron in the tissue specimens. Iron and erythropoietin are used to treat anemia in patients with renal insufficiency. It is plausible that in patients with renal insufficiency, a systemic "metallopathy" may exist that may predispose to the development of NSF. The exact role of gadolinium chelates in the pathogenesis of NSF has not been elucidated (at the time of writing).

NSF/NFD DUE TO GADOLINIUM USE IN PATIENTS WITH RENAL DYSFUNCTION: PLAUSIBLE HYPOTHESIS

Gadolinium-containing contrast media with a half-life of about 2 hours in patients with normal renal function are almost exclusively excreted by the kidneys. In patients with deranged renal function, the half-life of these agents is prolonged and may exceed 30 to 120 hours.[13] In addition, gadodiamide, a nonionic low-osmolar gadolinium agent possesses excess chelate (12 mg/mL).[14,21] The half-life of gadodiamide is prolonged (34.3 hours) in patients with end-stage renal disease compared with 1.3 hours in subjects with normal kidney function.[22] Dissociation of gadolinium agents by transmetallation with endogenous metals or acids leads to release of highly toxic, free gadolinium ions.[13,21] The free gadolinium may form salt precipitates with phosphates and carbonates that are then deposited in the interstitium of various organs including skin, muscle, bone, and liver.[13] Tissue deposition of gadolinium may then incite fibrotic reaction.

NSF/NFD: HOW DO WE DIAGNOSE THE CONDITION?

The epidemiological factors and distribution/morphology of the NSF dermopathy are fairly characteristic to permit a clinical diagnosis. The diagnosis is readily confirmed by histopathological examination of a deep skin biopsy specimen, the current standard criterion of diagnosis. Nephrogenic systemic fibrosis is histopathologically characterized by the proliferation of CD-34 positive dermal spindle cells, thick

collagen bundles with associated clefts and variable deposition of mucin and elastic fibers.[2]

NSF/NFD: HOW DO WE POSSIBLY TREAT THE PATIENTS?

Although several management strategies including skin-directed and systemic therapies have been described to control or reverse the condition, no definite effective therapy for NSF exists (as of today). It has been claimed that systemic treatment methods such as extracorporeal photopheresis, dialysis, plasmapheresis, and pharmacotherapy may stabilize or cure the condition.[8] The current best possible way to treat the condition is by early restoration of renal function, mostly by renal transplantation.[7]

NSF/NFD: WHAT CAN WE DO NEXT?

Given the putative association between gadolinium administration in patients with moderate or severe renal insufficiency and NSF, it is prudent to discuss the risks and benefits of a gadolinium-enhanced MRI study with the referring physicians and the patients.[6] In patients with moderate or severe renal insufficiency, it is advisable to avoid gadolinium agents, particularly gadodiamide, the agent that has been consistently documented in patients with NSF. Magnetic resonance imaging studies without gadolinium administration or alternative imaging techniques may be considered to answer the clinical question. In scenarios where the benefits of the gadolinium-enhanced MRI examination far outweigh the risks, use of lowest possible dose of gadolinium is recommended. Patients with renal insufficiency who receive gadolinium agents may benefit from a prompt hemodialysis, preferably within 3 hours of gadolinium administration.[19] The patients with renal insufficiency who receive gadolinium agents should be periodically monitored for symptoms and signs of NSF. Early, accurate diagnosis and prompt restoration of renal function are beneficial in patients with NSF. Physicians are strongly urged to report cases of NSF to the US FDA (http://www.fda.gov/medwatch/) and the NSF registry (http://www.icnfdr.org).

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