

NEPHROLOGY

Rounds®

Nephrogenic Systemic Fibrosis: What Nephrologists Need to Know

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Until recently, systemic fibrosing conditions have represented only a small niche in the spectrum of diseases encountered by nephrologists. In the last 10 years, however, a new disease entity has emerged: nephrogenic systemic fibrosis (NSF). Originally described as a "scleromyxedema-like cutaneous disease in renal dialysis patients," NSF was initially termed "nephrogenic fibrosing dermatopathy (NFD)" because of the dermal fibrosis that is a hallmark of the condition.¹ The term NSF gained wide acceptance after it was recognized that some patients with NFD have systemic involvement.²⁻⁴ This issue of *Nephrology Rounds* reviews several important aspects of NSF, including clinical presentation, histopathologic findings, its association with gadolinium (Gd), and potential therapeutic options. Unanswered questions and emerging concepts in the field are also highlighted.

Brief history and overview

NSF does not appear to have existed prior to 1997 when the first cases were recognized.¹ This observation led to the pursuit of an iatrogenic etiology for this condition. Like many newly-reported diseases, early NSF literature was limited to case reports or small case series.⁵⁻¹⁰ While important in documenting the clinical and pathologic characteristics of NSF, these uncontrolled reports were unable to identify risk factors for the disease. Further, NSF remained in the backwaters of medical literature because it was generally considered a rare condition of little clinical impact. In the last year, however, multiple reports have revealed an association between NSF and prior exposure to contrast agents that contain Gd,¹¹⁻¹³ which were previously considered to be safe in patients with kidney disease.¹⁴ In an upcoming report, Todd et al demonstrate that 24-month mortality is increased in outpatient hemodialysis patients with the cutaneous changes of NSF (48% versus 21%), with an adjusted hazard ratio of 2.9 (95% CI, 1.4-5.9).¹⁵ Thus, NSF has been thrust into the spot-light for nephrologists, radiologists, and indeed all those who care for patients with renal insufficiency.

The data presented in this issue are based on relatively small numbers of published reports on NSF, an amalgam of findings documented in case reports and case series, the largest of which include only 10-20 cases of NSF.^{1,11,13,16,17} To add to the confusion about this emerging condition, many case reports of NSF and potential advances in this field are reported in letters to editors, editorials, websites, or other forums not subject to the meticulous peer-review process required for original manuscripts.¹⁸⁻²¹ The paucity of peer-reviewed data limits our understanding of the disease and our ability to investigate additional disease associations, therapeutics, and outcomes.

Epidemiology

NSF is unique among the conditions that cause systemic fibrosis in that it invariably occurs in patients with kidney disease. As of December 2006, all of the cases of NSF reported to the official website of the US Food and Drug Administration (FDA) had occurred in patients with a glomerular filtration rate (GFR) <60 mL/min/1.73m² (http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200612HCP.htm) and most published cases have occurred in patients on dialysis or with GFR ≤15 mL/min/1.73m². NSF has been described in the settings of either acute or chronic kidney disease, as well as in either hemodialysis or peritoneal dialysis therapy.^{16,17} However, dialysis is not a requirement for NSF; approximately 10% of patients with NSF have never received renal replacement therapy in any form.²² NSF symptoms usually stabilize or even improve when renal function is restored, either through recovery of native renal function or from renal transplantation.^{7,17}

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The prevalence and incidence of NSF are difficult to determine because standardized diagnostic criteria do not exist. Some authors have attempted to estimate the incidence of NSF based on retrospective analysis of cases identified by other providers. For example, 3 cases of NSF were reported among a population of 467 dialysis patients over an 18-month period, with an incidence of 4.3 cases per 1000 patient-years.²³ However, these retrospective methods are flawed because they undoubtedly underestimate the incidence of NSF by relying on its recognition by outside providers who may or may not have experience with or knowledge about this emerging condition.²⁴

Ideally, estimates of prevalence and incidence would be determined based on a cross-sectional population-based study, in which investigators examined patients for clinical and pathologic evidence of NSF using pre-determined diagnostic criteria. Investigators have attempted just such a study in 186 outpatients receiving hemodialysis therapy.¹⁵ All patients were examined for cutaneous changes of NSF, defined using a scoring system that measures hyperpigmentation, hardening, and tethering of skin on extremities. Supportive skin biopsy was not pursued in this study in an effort to maximize patient participation, which was 94%. Cutaneous changes of NSF were present in 25 (13%) of the 186 patients, 4 of whom had prior skin biopsies available for review, each revealing the histologic changes of NSF. Although this provocative study did not show histologic evidence of NSF in all 25 patients, the findings strongly suggest that NSF is an under-recognized disorder and more prevalent than previously thought.

NSF occurs in patients regardless of age, gender, or race.¹⁵ Indeed, NSF has been reported in pediatric patients as young as 8 years old.^{7,22,25} Additional factors that do not appear to contribute to NSF are duration of renal dysfunction, hemodialysis membrane usage, and modality of dialysis (hemodialysis versus peritoneal dialysis).

Histopathology

Histologic analysis of NSF requires a full-thickness skin biopsy. Dermal thickening, increased collagen bundles, increased mucin, fibroblast proliferation, and spindle-shaped fibroblasts are well-described pathologic findings of the fibrosis.²⁶ Fibrosis can extend into the underlying subcutis, fascia, and even skeletal muscle,¹⁰ and dermal ossification has been described.²⁷ Samples stain positive for Factor XIIIa, CD34, CD45RO, CD68, procollagen I, and vimentin.^{2,16,22,28,29} Increased TGF- β mRNA in dendritic cells has been shown by *in situ* hybridization analysis.^{16,26} Cells in NSF lesions positive for CD34, CD45RO, and procollagen I may represent circulating fibrocytes.³⁰ These recently described cells are of hematopoietic lineage, but have acquired fibroblast-like properties. In patients with visceral involvement of NSF, similar fibrosis and immunologic staining patterns have been reported on biopsy or autopsy specimens from affected organs, including heart, lung, diaphragm, psoas, kidney tubules, rete testes, and dura mater.^{2,3,10,31,32}

Clinical presentation

Fibrosis dominates the clinical presentation of NSF.³³ It first affects the skin as dermal hardening with tethering to deep dermal tissues, giving the skin a wooden texture.

Figure 1: Typical skin changes of nephrogenic systemic fibrosis, with brawny induration, hardening, and tethering of skin to deep dermal tissues.



Patients often describe skin tightness, pruritus, a burning sensation, arthralgias, and myalgias in affected areas. Other skin findings can include brawny induration, hyperpigmented plaques, waxy erythematous papules, and subcutaneous nodules (Figure 1). Yellowish nodules on the sclera have also been described.⁹ For unknown reasons, NSF typically presents in the lower extremities at the calves in a symmetric fashion.³³ The fibrosis progresses proximally and distally to encompass the entire lower extremity. Upper extremity involvement also occurs frequently, but rarely without pre-existing or concurrent lower extremity disease. The trunk is involved less commonly and only late in extensive disease; the face is usually spared.³³

Similar to other conditions that cause skin fibrosis, advanced NSF can lead to joint contractures when fibrosis spans a joint.³³ These contractures are attributable to fibrosis of periarticular structures as opposed to erosive joint disease. Upper extremity involvement of the shoulders, elbows, wrists, and hands is a cause of functional disability. Importantly, joint contractures of hips, knees, and ankles can predispose patients to falling, and fractures are a concern in patients at risk for renal osteodystrophy.³⁴ Patients are reported to become wheelchair-bound.¹¹ Indeed, a history of new-onset falls in a patient with significant renal disease should prompt an examination for insidious NSF.

The potential severity of fibrosis and contracture that may occur in NSF is illustrated by the following anecdotal experience. At a hemodialysis center, this author was introduced to an elderly woman who was wheelchair-bound due to advanced NSF. She required four dialysis technicians to lift her from her wheelchair into her dialysis chair, one technician supporting each limb. Her extremities were fused to such an extent that she appeared to remain “seated” throughout the entire excruciating transfer from chair to chair.

Systemic fibrosis is an important and well-recognized feature of NSF.^{2,3,10,31,32} It occurs in a subset of patients who tend to have more extensive cutaneous disease, although the percentage of patients with systemic involvement is unknown. NSF has been reported to involve skeletal muscle, bone, lungs, pleura, pericardium, myocardium, renal tubules, rete testes, and dura mater.^{2,3,10,31,32} Diaphragmatic or pulmonary fibrosis may be implicated in respiratory failure and may cause features of restrictive lung disease.^{10,17,31}

The tempo of disease onset in NSF is variable and difficult to characterize because early NSF symptoms are often

overlooked or discounted by both patients and physicians. Rapidly progressive disease has been described, often with systemic involvement.¹⁰ It is more common, however, for patients to have a more indolent disease onset with several weeks to months of symptoms prior to diagnosis. Not all patients will progress to severe joint contractures with systemic involvement, although improvement in fibrosis is unlikely to occur except in the setting of improved renal function, when lesions are reported to improve.^{7,17}

Etiologies and associations

Since the initial descriptions of NSF, investigators have attempted to identify causative factors for the disease with the hope of limiting or eliminating them, if possible. They conjectured that some sort of new environmental, toxic, or iatrogenic exposure was a contributing factor, since NSF apparently did not exist prior to 1997.¹ However, determining the factors that may be involved in the pathogenesis of NSF eluded investigators until only recently. Initial cases of NSF appeared to be sporadic with no clear associations other than the fact that they only afflicted those with advanced renal disease. Many common epidemiologic factors are not associated with NSF.¹⁵ Further, alterations in hemodialysis or peritoneal dialysis techniques were unlikely to explain NSF because approximately 10% of such patients had not received dialysis therapy.²² Potential associations have also been suggested between NSF and endothelial injury (eg, thrombotic events, vascular procedures, or liver transplantation), but none of these have been formally evaluated.^{11,35,36} None of these associations, however, adequately explains the recent appearance of NSF.

As a result, investigators have focused their attention on new pharmacologic agents as potential causes for NSF. Many drugs have been implicated, including high-dose erythropoietin therapy,³⁷ lack of angiotensin-converting enzyme (ACE) inhibitor therapy,³⁸ and sevelamer,²⁵ but none have withstood or even undergone reproducible statistical analysis.

The gadolinium connection

Last year, Thomas Grobner of Austria first reported an association between NSF and the antecedent administration of gadodiamide (OmniscanTM, GE Healthcare, Princeton, NJ), a Gd-containing contrast material.¹² In this report, 5 patients with end-stage renal disease (ESRD) on hemodialysis developed clinical and histopathologic evidence of NSF only 2-4 weeks after receiving gadodiamide for contrast-enhanced, magnetic resonance imaging (MRI) study. Affected patients were also noted to be acidemic, although whether this coincided with disease onset was unclear. Grobner postulated that prolonged exposure to Gd-containing contrast allowed Gd to dissociate from its chelate and diffuse into tissues.³⁹ There, free Gd⁺³ would interact with anions such as phosphate and form precipitates in a process termed "transmetallation," which is toxic to rats.^{11,40,41} Acidosis may contribute because low pH promotes uncoupling of Gd-containing contrasts.^{11,14,40,41}

Although his report was based on only 5 patients, Grobner's hypothesis is an attractive one that addresses why NSF only afflicts patients with advanced renal insufficiency, regardless of dialysis modality, if any. Gd-containing contrast is rapidly excreted with a half-life of 1.3 hours in

healthy volunteers, but advanced renal insufficiency can extend this half-life to 30-120 hours.^{12,39} This hypothesis also adequately accounts for the recent appearance of NSF. Although Gd-containing contrasts have been available since the 1980s, their usage has only recently proliferated among patients with advanced renal insufficiency. A contributing factor is the historical belief that Gd-containing contrast agents are a safe alternative to iodine-containing radiographic contrasts in patients with renal disease.¹⁴ Furthermore, magnetic resonance angiography (MRA) and MR venography (MRV) use became widespread during the past decade. These imaging techniques typically require twice the quantity of contrast as conventional MRIs.¹¹ Patients with renal insufficiency are undoubtedly more likely to undergo these examinations, perhaps repeatedly, to assess vessels prior to fistula placement, transplantation, or because of concurrent peripheral vascular disease. This exposure may explain the apparent correlation between NSF and surgical procedures since patients with renal dysfunction are more likely to be exposed to Gd-containing contrast agents during MR vascular studies around the time of vascular procedures or organ transplantation.

Since Grobner's report, there has been a subsequent explosion in the number of publications addressing the association between NSF and prior exposure to Gd-containing contrast.^{11,13,24,42-51} Among the Gd-containing contrast agents, gadodiamide has the lowest conditional stability. This means that it has the least stable association between Gd and the chelate molecule at physiologic or more acidic pH.¹¹ This may explain why gadodiamide is the most commonly reported Gd-containing contrast agent implicated in NSF pathogenesis, although others have also been reported, including gadopentetate dimeglumine (Magnevist[®]; Berlex Imaging, Montville, NJ) and gadoversetamide (OptiMARK[®]; Mallinckrodt, St Louis, Mo).²⁴

Despite these new reports, many unanswered questions remain. Still unresolved is the risk posed by Gd-containing contrast agents in patients with advanced renal insufficiency. Retrospective analyses have reported the odds ratio for developing NSF after gadodiamide exposure to be 22.5 - 32.5,^{11,52} but the limitations of such retrospective analyses have already been outlined above. In their cross-sectional cohort study, Todd et al reported that the cutaneous changes of NSF were found in 16 (30%) of 54 patients with prior exposure to gadopentetate dimeglumine contrast. Such an exposure was associated with an increased risk of developing the cutaneous changes of NSF (OR 14.7, 95% CI, 1.9 - 117.0, compared with nonexposed patients).¹⁵

Clearly, not all patients with renal failure develop NSF upon exposure to a Gd-containing contrast agent, therefore what other factors predispose to NSF? We do not know. Notably, acidosis has not been universally described as an associated risk factor for NSF in the setting of Gd-contrast exposure.⁵² In order to correlate these variables, blood pH must be recorded at the time of exposure to Gd-containing contrast, not days before or after. Further, it remains to be shown whether the onset of NSF absolutely requires exposure to Gd-containing contrast material. One report was unable to identify any such exposure within the 6 months prior to NSF onset,⁵³ but patients may unknowingly be exposed to Gd-containing contrast in procedures

other than MRI, such as computer tomography (CT) scan or conventional angiography. One group has suggested that Gd-carrying chelates, not Gd itself, may be the driving factor in NSF pathogenesis.⁵² However, electron microscopy has recently revealed the presence of insoluble Gd and calcium phosphate deposition in a skin biopsy specimen from a patient with NSF, strengthening the Gd argument.⁴²

The US FDA has become aware of the association between NSF and exposure to Gd-containing contrast agents in patients with advanced renal disease. In June 2006, an FDA statement advised: “physicians should carefully assess the need for performing MRI with contrast in patients with advanced renal failure (those currently requiring dialysis or with GFRs ≤ 15 mL/min/1.73m²) and administer the minimal required dose of contrast agent if MRI contrast is necessary” (<http://www.fda.gov/cder/drug/InfoSheets/HCP/gccaHCP.pdf>. Accessed May 29, 2007). Further review by the FDA found that “as of December 21, 2006, 90 individuals with NSF/NFD had been reported to the FDA; all had moderate (GFR < 60 mL/min/1.73m²) to end-stage renal disease (GFR < 15 mL/min/1.73m²) prior to an MRI or MRA with a Gd-based contrast agent.” (http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200612HCP.htm. Accessed May 29, 2007). The FDA has thus recommended that in patients with GFRs < 60 mL/min/1.73m², alternative imaging methods or contrast agents be chosen whenever possible.

In the event that patients with this degree of renal impairment are exposed to Gd-containing contrast, prompt hemodialysis can be considered, since 99% of Gd-containing contrast can be cleared by three, standard, 4-hour, 3-times weekly hemodialysis sessions.⁵⁴ However, this approach appears to be insufficient to eliminate the risk of NSF. In a sobering report, NSF occurred even in patients who underwent 3 daily hemodialysis sessions following gadodiamide exposure.¹¹ Given these findings, it is advisable to avoid as much as possible the use of Gd-containing contrast agents in patients whose GFRs are < 15 mL/min/1.73m². If a contrast-enhanced MRI is deemed absolutely necessary, then a Gd-containing agent other than gadodiamide is strongly recommended and, even in that case, the minimum amount of contrast necessary for the study should be administered. The patient should be informed about the risk for NSF and followed for any evidence of disease development. In a patient with established NSF and no anticipation of improved renal function, Gd-containing contrast agents should be considered contraindicated.

Differential diagnosis

Clinical, laboratory, and histopathologic findings allow NSF to be distinguished from other systemic fibrosing conditions (Table 1). Of course, all patients with NSF have advanced renal dysfunction, a feature unique among fibrosing disorders and the distribution of fibrosis is often informative.³³

Table 1: Differential diagnosis of fibrosing conditions	
Condition	Distinguishing features
Nephrogenic fibrosing dermatopathy	Advanced renal insufficiency Primarily involves extremities Yellow plaques on sclera
Scleroderma	Facial involvement CREST features ³² Anticentromere or anti-SCL70 antibodies
Scleromyxedema	Facial involvement Paraproteinemia
Scleredema diabeticorum	Diabetes Primarily involves upper torso and back
Pretibial myxedema	Hypothyroidism
Lipodermatosclerosis	Involves lower extremities exclusively Does not cause joint contractures
Eosinophilic fasciitis	Eosinophils on skin biopsy
Porphyria cutanea tarda	Involves sun-exposed skin
Eosinophilic myalgia syndrome ⁵⁴	Exposure to contaminated L-tryptophan
Spanish toxic oil syndrome	Exposure to contaminated rape seed oil ⁵⁴
Graft-versus-host disease	Transplantation recipient
Post-radiation fibrosis	Involves radiation-exposed skin

CREST: calcinosis, Raynauds, esophageal dysmotility, sclerodactyly, telangiectasia

In the workup of NSF, laboratory analysis can exclude some causes of systemic fibrosis. Although low-titer antinuclear antibodies have been reported in patients with NSF, the anticentromere antibodies and anti-SCL70 autoantibodies of scleroderma are not present.²⁶ Scleromyxedema occurs in the setting of paraproteinemia, which can be assessed by serum protein electrophoresis.²⁹ Pretibial myxedema from prolonged hypothyroidism can be distinguished easily by testing thyroid function.

Skin biopsy can provide additional data to separate NSF from other fibrosing conditions. Unlike eosinophilic fasciitis (Shulman’s syndrome) and eosinophilic myalgia syndrome, eosinophils are not a dominant feature of NSF. In general, NSF skin biopsies lack the infiltrating plasma cells of scleromyxedema.⁵ However, a recent clinicopathologic study concluded that NSF and scleromyxedema were difficult to distinguish based solely on histologic findings.²⁹ More useful features were clinical evidence of renal failure, distribution of fibrosis, and the presence or absence of paraproteinemia. This study calls into question any claim that a skin biopsy should be the “gold standard” for the diagnosis of NSF.

Additional non-fibrosing conditions that preferentially afflict patients with renal failure might cursorily be mistaken for NSF. Tense lower extremity edema may cause brawny skin changes, but joints are not

contracted, pitting is still present on examination, and the underlying dermis remains malleable. Calciphylaxis can cause localized scarring with reactive fibrosis, but NSF does not cause the ulcerating skin lesions seen in calciphylaxis. These conditions have been described concurrently, however.^{10,28} Dialysis-associated β -2 microglobulin (β 2m) amyloidosis can occur in patients on chronic dialysis therapy and results from the accumulation and deposition of β 2m systemically, particularly in joints and periarticular tissues.³⁴ Accordingly, this condition presents primarily as an arthropathy, not as skin fibrosis and only after years of dialysis therapy.⁵⁶ In addition, the prevalence is on the decline in countries where high-flow dialysis machines are commonplace. Finally, neuromyotonia can cause the extremities to become so rigid that the changes can be mistaken for fibrosis. However, examination reveals relatively supple superficial skin with underlying musculature rigidity; electromyography confirms the diagnosis.

Diagnosis

The diagnosis of NSF requires appropriate considerations of clinical and laboratory data. Clinical findings of cutaneous or systemic fibrosis in a patient with advanced renal dysfunction should prompt examination for NSF. Often, physical examination and laboratory analysis are adequate to make the diagnosis of NSF and exclude other common conditions causing systemic fibrosis. Recent administration of Gd-containing contrast may be supportive, but it remains unclear whether all patients with NSF have such an exposure history. Certainly, NSF does not develop in every patient with renal failure exposed to Gd-containing contrast. If doubt remains as to the diagnosis, then supportive evidence can be provided by imaging studies or deep tissue (full-thickness) skin biopsy. Non-Gd enhanced MRI may reveal skin thickening and elevated T_2 signals in muscle mimicking inflammatory myositis.¹¹ Scintigraphic bone scan can show increased radiotracer uptake in affected skin, muscle, and tendons.¹¹ Interestingly, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has shown increased metabolic activity in affected skin.⁵⁷ If needed, skin biopsy can further support the clinical diagnosis, but is not required. The need for histologic evidence of NSF should be weighed against the potential for less than trivial infectious complications of a full-thickness (often lower-extremity) skin biopsy in patients with renal insufficiency and, often, diabetes mellitus or peripheral vascular disease. Accordingly, such a biopsy should be performed only by dermatologists, surgeons, or those providers experienced with the procedure.

Treatment

For all patients afflicted with NSF, physical therapy is advisable as an effort to maintain joint mobility.³³ Unfortunately, aside from an improvement in renal function, no treatment modality has proven reproducibly effective in NSF. An effective therapy would need to show improvement in skin and systemic

fibrosis, while documenting negligible improvement in renal function. Many pharmacologic agents and other methods have been attempted and published at the case report level, including corticosteroids,^{4,22} thalidomide,^{29,33} cyclophosphamide,^{29,33} mycophenylate mofetil,²² intralesional methotrexate,⁶ intravenous immunoglobulin,⁵⁸ plasmapheresis,^{4,5} and plasma exchange.⁶ Clearly, case reports are uncontrolled and, while some of these cases do claim improvement in skin fibrosis (eg, after plasmapheresis), renal function either improves or is not reported. One treatment modality, extracorporeal photopheresis, has shown more promise than the others and may be advisable in early-onset, rapidly-progressive NSF;^{22,42,59} however, it is expensive, time-consuming, and likely not covered by third-party payers. What treatment options might exist on the horizon? Investigators have shown that imatinib mesylate (Gleevec[®]) reduces fibrosis in mice receiving subcutaneous injections of bleomycin, a well-established model of fibrosis.⁶⁰ Whether imatinib mesylate has any benefit in humans with NSF remains unknown.

Conclusions

Nephrogenic systemic fibrosis represents a serious emerging disease among patients with advanced renal insufficiency. New-onset pain and stiffness of the extremities should prompt an evaluation for dermal and systemic fibrosis. Clinical history, physical examination, and a few lab tests are sufficient to make a diagnosis in most cases, although additional imaging studies or full-thickness skin biopsy can be considered in ambiguous cases. NSF is likely more prevalent than previously appreciated, and exposure to Gd-containing contrast agents appears to be a risk factor for disease onset. Importantly, patients with the cutaneous changes of NSF appear to have increased mortality compared to unaffected patients with renal disease. Although the number of publications on NSF has been limited, the growing volume of quality peer-reviewed literature continues to add to our knowledge of this mysterious condition. Further, clinicians who encounter cases of NSF should report them to the US FDA by phone (1-800-FDA-1088) or through the web-based MedWatch reporting program (<http://www.fda.gov/medwatch/>), or through the appropriate non-US regulatory agency.

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