

# Nephrogenic systemic fibrosis

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## Abstract

Nephrogenic systemic fibrosis, initially called nephrogenic fibrosing dermopathy, has been strongly linked to exposure to gadolinium-based contrast media used in magnetic resonance imaging in patients with renal insufficiency. This review discusses recent advances in our understanding of the pathophysiology and clinical approach to patients with chronic kidney disease who require diagnostic imaging with gadolinium-based contrast media.

## Introduction and context

Nephrogenic systemic fibrosis (NSF), initially named nephrogenic fibrosing dermopathy, was first reported in 2001 by Cowper *et al.* [1]. The earliest known case of NSF developed in January 1997. Since then, more than 360 cases have been tracked by the Yale International NSF Registry [2] and over 500 cases have been reported to the US Food and Drug Administration MedWatch database. NSF occurs most often in middle-aged adults (mean age of 52 years) with either chronic kidney disease or acute kidney injury but has also been observed in children and older patients. NSF usually manifests approximately 2-10 weeks (median 5 weeks) after exposure to gadolinium-based contrast agents (GBCAs). There is no gender or racial predisposition.

Of NSF cases reported to the Yale Registry, all have occurred in patients with renal insufficiency. In recent years it has become clear that NSF is also associated with fibrotic damage to internal viscera such as the esophagus, lungs, heart, skeletal muscle, and kidneys (prompting a change in name from nephrogenic fibrosing dermopathy to nephrogenic systemic fibrosis). In some cases NSF has contributed to the death of the afflicted individual. By 2007, it became apparent that the common factor in most patients was the prior use of GBCAs during magnetic resonance imaging, however, in many cases (e.g., when imaging brain tumors), the use of GBCAs are critical for enhancing the imaging of blood vessels.

The basic clinical features of NSF include acute to subacute onset of limb edema (more so in the lower limbs) accompanied by cutaneous erythematous to violaceous papules and plaques overlying dermal and subcutaneous fat fibrosis. When fully developed, clinical NSF is characterized by limb pain, contractures, and loss of mobility. The clinical syndrome strongly mimics scleroderma and eosinophilic fasciitis, and may be rapidly progressive. Yellow scleral plaques mimicking pingueculae are often present in affected patients.

NSF has specific clinical and histopathologic characteristics that should be used to make a definitive diagnosis. Histologic features include a haphazard arrangement of thickened collagen bundles, mucin deposition, and an increase in fibroblast-like cells that stain positively for CD34 and procollagen I, the same immunohistochemical profile as that of 'circulating fibrocytes' (which play an important role in disease development). This abnormal pathology extends into the fibrous septa between fat lobules, contributing to the typical clinical manifestation of woody induration and a 'peau d'orange' or 'cobblestone' skin surface appearance. It has been hypothesized that this pathology is the effect of the bone marrow-derived circulating fibrocytes (normally recruited to repair injured tissue) behaving in an exuberantly abnormal fashion in the dermis and fibrous septa of the subcutaneous fat.

### Recent advances

To date, the Yale Registry indicates that at the time of disease onset, 79% of patients with NSF were receiving renal dialysis and 17% had some degree of renal insufficiency but were not being dialyzed (those with acute kidney injury, unspecified renal insufficiency, or chronic kidney disease stage IV or V). The remaining patients were in the immediate post-renal-transplant period (Cowper, unpublished data).

Experimental data suggests that when gadolinium, a rare earth element that is naturally highly toxic to animals and humans, is bound to proprietary chelating agents, it is essentially biologically inert in the circulation of a patient with normal kidney function (in whom the half-life would be roughly 90 minutes) [3]. Since GBCAs are cleared from the body virtually exclusively by the kidneys, the current hypothesis is that individuals with reduced renal clearance are exposed to these agents longer than those with normal renal function, which can lead to NSF in the vulnerable, however, the exact pathogenic mechanisms remain unknown.

Because gadolinium is not normally ingested by humans, radiologic examinations where GBCAs are administered are the only significant source of human exposure. Several pharmaceutical companies produce a variety of GBCAs, which are distinguishable by their varying proprietary chelating agents (ligands). The ligands are classified as structurally linear or macrocyclic and exhibit both ionic and non-ionic forms. The macrocyclic gadolinium-ligand complexes are less prone to 'dechelation' (which would render the GBCA potentially toxic) and are therefore more stable than the linear non-ionic agents. This is thought to be the underlying reason why macrocyclic agents are only rarely associated with NSF. Interestingly, even among the linear agents there may be differences in propensity to trigger NSF between ionic and non-ionic varieties.

In the event of dechelation, ionic gadolinium ( $Gd^{3+}$ ) quickly binds to ubiquitous phosphate, forming insoluble gadolinium phosphate and leading to prolonged exposure to biologically active gadolinium. With gadolinium no longer circulating, it cannot be significantly removed by dialysis. Complicating the situation is that, over the years, various GBCAs have been used interchangeably and patients' charts typically do not necessarily reflect which brands were administered, making it very difficult to retrospectively pinpoint the precise agents used. The risk of NSF is estimated to be between 2% and 6% in patients with chronic kidney disease (stage IV and V) and acute kidney injury, with the

most risk associated with higher degrees of impairment and less effective modes of clearance (i.e., peritoneal dialysis) [3].

A recent change in FDA labeling of GBCAs suggests the linear non-ionic agents (OptiMARK and Omniscan) as well as the most widely-used linear ionic agent (Magnevist) be specifically contraindicated in the setting of renal disease. The warning requires that screening (medical history and/or laboratory tests) be conducted for renal dysfunction prior to the administration of GBCAs [4]. These recent labeling changes are in line with recommendations already made by the European Medicines Agency and the American College of Radiology. Since the FDA black box warnings were first issued in 2007, the incidence of new cases has dropped from 36.5 cases per 100,000 to 4 cases per 100,000 [5].

In general, treatment of NSF using topical steroids, immunosuppressive therapy, and plasmapheresis has been ineffective. Several studies have described anecdotal treatments that may improve NSF, including ultraviolet-A exposure, pentoxifylline, sodium thiosulfate, photopheresis, and rapamycin, however, these studies suffered from small numbers, no controls, and sometimes a lack of peer review. Recent data presented by Jonathan Kay [6] at the Fourth Annual Symposium on Nephrogenic Systemic Fibrosis and Gadolinium-based Contrast Agents demonstrated that imatinib mesylate improved skin tethering and thickening as judged by the Rodnan skin score. However, all of the patients in the study relapsed after the drug was discontinued and it has not yet been determined whether the noted beneficial effects were related to a reduction in interstitial edema or a partial reversal of the fibrosis. The second-generation drugs dasatinib and nilotinib are currently in the queue to be evaluated.

High *et al.* [7] at the University of Colorado used energy dispersive spectroscopy, X-ray microscopy, and inductively coupled plasma mass spectroscopy to detect gadolinium in skin and other tissues from patients with NSF. However, based on their studies, a high tissue level of gadolinium is not necessarily sufficient to produce NSF by itself. They also showed that gadolinium could be displaced ('dechelated') from its ligand in the presence of another metal such as iron or zinc. This 'transmetallation' would result in free ionic gadolinium (which, as noted above, would be very likely to form insoluble gadolinium phosphate) and a ligand complex with iron, zinc, or another displacing metal. Factors which facilitate transmetallation are high or low blood pH levels, endothelial injury, inflammation, and high

phosphate levels, all of which are present in the tissue milieu of patients with renal insufficiency [8]. High *et al.* [7] also showed that the tissues with the highest levels of gadolinium are associated with the most severe fibrosis in the skin and other organs such as the heart, lungs, lymph nodes, eye tissues, muscle, and liver. Synchrotron X-ray fluoroscopy also has been used successfully to detect gadolinium in tissues [8].

#### Basic science

NSF is the only fibrosing disorder where the trigger is essentially known but the pathogenic mechanisms have yet to be fully clarified. NSF can also serve as a model to gain an understanding of the pathways responsible for idiopathic fibrosing disorders in other organ systems. Current investigation into NSF has revealed that *in vitro* GBCAs stimulate fibroblasts from patients with NSF (and those from normal controls) to secrete increased amounts of extracellular matrix, hyaluronic acid, and collagen. However, serum from patients with NSF also stimulates fibroblasts to secrete increased amounts of these same substances. Serum from dialysis patients behaves similarly but not to the same magnitude. In rats, some linear GBCAs stimulate fibroblasts to proliferate and caused normal fibroblasts to transform into myofibroblast-like cells with a phenotype similar to that of differentiated fibroblasts present in NSF lesions. Chelating agents alone (*sans* gadolinium) did not produce these effects. Therefore, free gadolinium is the most obvious suspect in promoting NSF [9,10].

Fibrocytes, circulating bone marrow-derived mesenchymal stem cells, also accumulate in NSF lesions, where they further differentiate into fibroblasts and myofibroblasts. Increased sensitivity of NSF fibrocytes to gadolinium has been shown in various experiments [11,12].

In another rat model, gadolinium produced skin lesions but the chelating agents did not. It is clear that the stability of the GBCA complex is the most important factor, thereby implicating free gadolinium as the culprit in inducing the disease and absolving the chelating agents [13]. In studies of renally insufficient rats, linear non-ionic GBCAs produced the most gadolinium deposition in the skin, which was further promoted by high tissue levels of phosphate [14].

Animal models have provided further evidence for the role of other molecules in NSF. The first is osteopontin, a multifunctional protein first identified in bone but present in virtually all tissues. A major modulator of processes involving fibrosis and wound repair, osteopontin was found to be elevated in an experimental gadolinium-induced rat model of NSF [15]. Additionally,

Cox [16] created a gadolinium-induced rat model of NSF in which an experimental anti-platelet-derived growth factor receptor compound, as well as the cancer drug imatinib, were both effective in preventing and reversing fibrosis.

#### Implications for clinical practice

Recent reports have indicated that patients at the highest risk for NSF have chronic kidney disease stages IV or V and that no cases have been observed in patients in earlier stages thus far [17,18]. Similarly, patients with acute kidney injury appear to be susceptible to NSF. Therefore, careful screening of patients for underlying kidney disease or severe injury using measurements of serum creatinine and other appropriate tests of renal function (the choice of which depends on medical history and physical examination) should decrease the risk of NSF in patients receiving GBCAs. Keeping a careful history of previous exposure to a GBCA, both in time and dose, would assist in GBCA selection and in calculating an appropriate dose to be administered. Post-imaging dialysis has also been proposed as a way to mitigate the development of NSF in certain high-risk patients by removing circulating GBCA in a more timely manner. Currently, this is recommended only in cases in which the patient is already receiving hemodialysis. For those not being dialyzed, or those on peritoneal dialysis, no specific recommendations exist.

#### Abbreviations

GBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

#### Competing interests

The authors declare they have no competing interests.

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