

From the pages of

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shedding light on the effects of retained gadolinium from Contrast MRI

Background on NSF

Although it was not known at the time, evidence of a problem related to Gadolinium-Based Contrast Agents ([GBCAs](#)) first appeared in 1997 in a group of 15 renal dialysis patients in California. The cases were first described in the literature in 2000 as a scleromyxoedema-like dermatopathy that was characterized by thickening and hardening of the skin of the extremities.¹

Because the disease was thought to be a new fibrosing skin disorder that affected patients with severely impaired renal (kidney) function, it was named Nephrogenic Fibrosing Dermopathy (NFD).² The cause was unknown.

The first cases in 1997 were investigated by The Centers for Disease Control and Prevention (CDC) and doctors from the University of California in San Francisco including Dr. Philip LeBoit and Dr. Shawn Cowper. In 2001, Dr. Cowper moved to Yale University School of Medicine and the investigative effort also moved to Yale. Dr. Cowper is currently in charge of confirming and investigating cases of NFD/NSF. He also maintains the NSF Registry which is a repository of information about patients with NSF from around the world.³

By 2003, further evaluation including autopsies on deceased NFD patients, found that the damage caused by the disease went far beyond the patients' skin and involved internal organs and tissues.^{4,5,6} The name was then changed to Nephrogenic Systemic Fibrosis (NSF) to reflect the systemic nature of the disease.⁷

In 2006, Dr. Thomas Grobner of Austria first made the connection between Gadolinium-Based Contrast Agents administered for MRI and the disease currently known as NSF.⁸ That same year Dr. Peter Marckmann and colleagues published their study that also confirmed the connection.⁹

Various treatments for NSF have been tried, but none have been consistently successful.³ While some NSF patients have seen improvement of their skin changes and joint contractures, NSF still remains an incurable and potentially life-threatening disease.

Since 1997, when problems first appeared, much of the research has been focused on trying to determine how and why NSF/NFD happened only in renally-impaired patients. Although NSF is known to be a systemic disease, the diagnosis is still primarily based on skin changes and "visible" evidence of a Gadolinium-related problem in patients with severe kidney disease.^{10,11,12}

Diagnosing NSF

Since NSF was first described in the literature, most papers have focused on the skin manifestations of the disease as it was seen in severely renally-impaired patients. Page 14 of a December 8, 2009, FDA

Advisory Committee Briefing Document¹³ provides information from Cowper et al (2008) regarding skin involvement. Skin lesions are often symmetrical and bilateral, and found to be localized in decreasing order of frequency to the lower extremities (85%), upper extremities (66%), trunk (35%), hands (34%), feet (24%), buttocks (9%), and face (3%).¹⁴

The clinical diagnostic criteria for NSF include: patterned plaques, joint contractures, “cobblestoning”, marked induration/Peau d’orange, puckering/linear banding, superficial plaques, dermal papules, and scleral plaques. Histologic findings include: increased dermal cellularity, CD34⁺ cells with tram tracking, thick and thin collagen bundles, preserved elastic fibers, and septal involvement. Osseous metaplasia is a highly specific finding in NSF.^{15,16} Some authors have suggested that osseous metaplasia may represent a late, involuting stage of NSF.¹⁷

However, even among renally-impaired patients, skin findings are not uniform. NSF has presented as a progressive myopathy or muscular disease, with minimal skin findings, in a patient with acute renal failure.¹⁸ It has been reported that the skin manifestations in the late stages of NSF are different from those seen early in the disease and have a varied presentation.^{19,20,21}

A 2011 Japanese study suggested the occurrence of a non-plaque, late-onset type of NSF in patients who presented glossy, smooth skin with gradual hardening of the skin. That group’s symptoms were reported to develop after a longer time period since their last exposure to Gadolinium. The authors suggested that the “late-onset of NSF may be explained by the slow release of free Gadolinium from bone stores”. In Japan they generally administer a smaller dosage of the GBCA.²² If less Gadolinium is being retained, it might explain some of the differences in the clinical manifestations.

Since there are differences seen among renally-impaired patients, it would seem that there might also be differences seen between the renally-impaired and non-renally-impaired if less toxic Gadolinium is retained.

It is also possible that the damage is being done of the inside of the patient and not readily seen with the naked eye regardless of the patient’s level of renal function. (See [Background on Gadolinium](#) for more information.)

NSF – It’s not caused by the kidneys.

It is now widely recognized by the medical community and government agencies that retained [Gadolinium](#), and not impaired kidney function, is the primary contributor to the development of NSF.

Rheumatologist Dr. Jonathan Kay suggested that the disease be called Gadolinium-Associated Systemic Fibrosis or GASF, since as he said, “NSF neither originates in the kidney nor is caused by factors originating in the kidney”.²³ It’s the Gadolinium in tissue that seems to drive the fibrosis.²⁴

Studies have shown that all GBCAs and Gadolinium Chloride (GdCl³⁺) stimulate fibroblast proliferation in tissue taken from healthy subjects.^{25,26,27,28} (Fibroblasts play a role in the production of connective tissue and fibrosis.) There is a growing body of research that provides evidence of Gadolinium or its toxic effects also being found in bone and tissue of study animals and humans with normal renal function.^{29,30,31,32,33,34,35,36,37}

Since at least 1992, dechelation or separation of the GBCA complex due to transmetallation and acid dissociation was confirmed in animal studies.³⁸ Human *in vivo* comparative studies confirmed transmetallation occurs in healthy humans.^{39,40} Other than kidney impairment, researchers have said that transmetallation poses the greatest potential risk for the release of the toxic metal ion from the

chelate.^{41,42} (Transmetallation is the displacement of the Gadolinium ion (Gd^{3+}) from the chelate by other metal ions in the body such as zinc, calcium, iron and copper.)

Besides transmetallation, there are other factors that can increase the risk of retaining Gadolinium including in patients with normal kidney function. Those risk factors include acidosis, transient acute kidney injury (AKI), recent surgery, inflammatory events, abnormal vascularity, and compromised blood-brain barrier. Cumulative dosage from multiple contrast MRIs or MRAs is thought to be another risk factor. (See [Risk Factors](#) for details.)

In 2007, the FDA requested a “boxed warning” be added to all GBCA product labeling that stated that patients with severe kidney insufficiency were at risk of developing NSF.⁴³ In 2010, the FDA required that GBCAs carry new warnings on their labels about the risk of NSF. Three GBCAs – Magnevist, Omniscan and Optimark – were described as “inappropriate for use among patients with acute kidney injury or chronic severe kidney disease”. The FDA said that all GBCA labels will emphasize the need to screen patients to detect these types of kidney dysfunction before administration.⁴⁴

Since the FDA instituted the new screening and use guidelines in renally-impaired patients, there have been far fewer new cases of NSF. However, based on the published medical literature and our Self-Study reports, it appears that patients with normal kidney function may also be at risk of retaining Gadolinium and experiencing symptoms of Gadolinium Toxicity.

The urine test results presented in our [Self-Study of Retained Gadolinium](#) and Appendix 1 of the [Symptom Survey Report](#) show patients with no history of kidney problems excreted elevated urine levels of Gadolinium for extended periods of time after their last dose of a GBCA. Based on the published literature, that should not happen to patients with normal kidney function (meaning eGFR >60).

To our knowledge, there are no published cases of biopsy-confirmed NSF in patients with normal kidney function, but that does not mean that Gadolinium-related health issues cannot occur in those patients. Since residual Gadolinium from GBCAs has been found in bone and other tissue of study animals that did not have NSF-like skin lesions,^{45,46,47,48} it would seem that patients might not always present clinically with visible evidence of a problem. Currently, there are no established criteria to evaluate patients for other signs of Gadolinium Toxicity beyond the skin changes associated with NSF. That could result in the underreporting of Gadolinium-related health issues in all populations of patients.

While there appear to be many unanswered questions related to Gadolinium-Based Contrast Agents, what is known from the literature is that Gadolinium is toxic to humans and published studies have found evidence of Gadolinium in brain, bone and skin tissues of patients without severe kidney disease.^{36,37,49,50,51}

Anyone who has unexplained symptoms that they believe were caused by retained Gadolinium from a contrast MRI or MRA should report it to the FDA by filing a MedWatch Adverse Event Report. Call 1-800-FDA-1088 or report via the FDA website at <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>

It is important that Adverse Event Reports related to Gadolinium-Based Contrast Agents are filed with the FDA or the full scope of Gadolinium-related health problems may never be brought to light.

Patients outside the U.S. report to their country’s equivalent governing agency.

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