SR
SCIENTIFIC REVIEW
E.P.C.M.S.

Nephrogenic Systemic Fibrosis: Why Should We Be Concerned? Part 1

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The pure and simple truth is rarely pure and never simple
- Oscar Wilde

Nephrogenic Systemic Fibrosis (NSF) is a rare, debilitating, fibrosing disorder that occurs in patients with chronic or acute renal failure. It was first described in 2000 as a sclero-myxedemea like cutaneous illness in patients on chronic hemodialysis[1] and later known as a nephrogenic fibrosing dermopathy[2] because of its predominant cutaneous manifestations. However after the identification of significant systemic involvement of other internal organs the name was changed to NSF.[3-9]

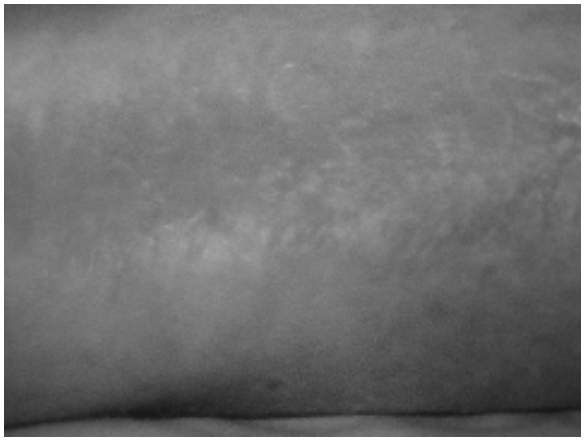
NSF is increasingly accepted as an iatrogenic disorder noted after intravenous exposure to gadolinium containing contrast agents (GCCA) used for radiological studies.[10,11] Other factors may also be involved but if a patient has renal failure, avoidance of GCCA or alternative imaging studies should be considered.[10-19]

Numerous warnings and reviews on NSF have been published[4,6,8,19-25,29-37] Notwithstanding these, nowadays, there are at risk renal patients that unknowingly receive GGCA, when it is not indicated. This eclectic review is an update of current NSF knowledge and how to prevent it. The first part includes: 1) Case Reports of NSF noted in El Paso; 2) Epidemiology; 3) The Stages of Chronic Kidney Disease; 4) Overview of Gadolinium, Chelates, Transmetallation and Federal Drug Administration (FDA) warnings; 5) The Clinical Manifestations of NSF; 6) Risks Factors and NSF mnemonic; 7) Pathogenesis. The second part of this article will review: 8) Diagnosis; 9) Differential Diagnosis; 10) Prognosis; 11) Prevention; 12) Treatment; 13) Summary and 14) The Good, The Bad and The Ugly of NSF.

1. CASE REPORTS

Case 1. 68-year-old Hispanic female with end stage renal disease (ESRD) secondary to diabetic and hypertensive nephrosclerosis on hemodialysis for nine years. She had required multiple admissions for problems related to failed dialysis angioaccesses and neurological problems. During this lapse she was investigated for problems related to sepsis, altered mental status and myoclonic jerking of upper extremities. Her work up required three magnetic resonance imaging (MRI) studies, two in 2002 (brain and neck vessels) and one brain MRI in 2004 using Magnevist.® Throughout her management she was treated several times for catheter related infections. Over the years she developed doughy edema and erythema (Image A) progressive muscle atrophy and joint pain and was ultimately confined to a wheelchair. She also exhibited the diabetic sequelae of retinopathy, peripheral neuropathy, peripheral vascular disease and deconditioning. Computed tomography (CT) scans showed old atrophic changes and microvascular disease. The MRI showed findings suggestive of a right embolic infarct. Her clinical course progressed downhill and she was diagnosed with NSF in 2009. Subsequent labs showed a hematocrit of 40, white cell count of 3900, BUN 35 mg%, creatinine 4.4mg%, phosphorus 6.4 mg%, calcium 11mg%, sodium 137 mEq/L. On her last admission she sustained a myocardial infarction with refractory hypotension, developed advanced NSF and expired.

Image A



Case 2. 48-year-old Native American male with a longstanding history of multiple medical comorbidities such as polyneuropathy, systemic vascular disease, end stage renal disease secondary to diabetic nephropathy and hypertension. He was on hemodialysis for six years and had gram negative bacteremia with Pseudomonas aeruginosa which resolved with antibiotics and the replacement of the hemodialysis catheter. On August 2004 he was admitted for evaluation of metabolic encephalopathy with vertigo, nystagmus and an unsteady gait. Both lumbar puncture and MRI of the brain with and without contrast following the injection of Magnevist® showed no abnormalities. He received a coronary artery bypass in 2007. He subsequently presented with bilateral doughy indurated lesions of both shins. In 2008 due to severe peripheral vascular disease complicated with non healing left heel ulcers and chronic osteomyelitis, he required a below the knee amputation. Afterwards, he developed progressive ascites, pleural effusions and respiratory failure of unknown etiology requiring multiple paracenteces and ultimately expired in 2009 with multiple organ failure. The clini-

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cal findings were consistent with NSF and confirmed later, on second review, by the pathologic studies from the below the knee amputation which were also consistent with NSF.

Case 3. 56-year-old Hispanic female with ESRD secondary to chronic glomerulonephritis and hypertension on hemodialysis for three years after a failed kidney transplant. In 2008 she had a cerebro vascular accident (CVA) and underwent an MRI of the brain with GCCA. She was later investigated for a 4 day history of increasing nausea, vomiting and abdominal pain with a CT and enhanced MRI of the abdomen with GCCA. These studies revealed moderate renal atrophy with multiple bilateral renal cysts, a prior cholecystectomy and a failed left iliac fossa kidney transplant. The white cell count was 21,000, hematocrit 34.8%, potassium 5.7 mEq/l, BUN 85 mg%, creatinine 6.25 mg%, albumin 3.4, intact PTH 170 pg/ml. Over the following year she developed progressive deconditioning, doughy edema and flexion contractures of her feet and hands (Image B). She became hypoxic requiring oxygen therapy and was recently diagnosed as having pulmonary fbrosis. She was diagnosed with NSF in California before her transfer to El Paso.

Case 4. 79-year-old Caucasian female with ESRD from diabetic and hypertensive nephrosclerosis, on maintenance hemodialysis for four years. She had severe atherosclerotic coronary artery disease and required angioplasty and stent deployment. She also presented with a transient ischemic attack (TIA) during dialysis and required an MRI with Magnevist® on February 2005 that showed bilateral stenotic carotid lesions. Later, another MRI with Magnevist® on May 2006 was done to rule out TIA versus infarct that showed periventricular and right insular small vessel ischemic changes without evidence for mass or acute infarct. In the ensuing years she required multiple admissions for progressive fluid overload with bilateral pleural effusions, pulmonary fibrosis, pulmonary hypertension, recurrent episodes of atrial fibrillation and pulmonary edema. By 2007, she also developed progressive indurated edema and chronic arthritic deformities with contractions. This led to progressive immobility and disability and she was confined to a wheelchair and bed. Her work up for collagen vascular disease and scleroderma was negative. She had a skin biopsy that was non diagnostic for scleroderma and NSF was finally diagnosed by history of exposure to GCCA and exclusion of other disorders.

2. Epidemiology:

Before 1997 instances of NSF were not reported. There has since been a change in radiological practices and the subsequent use of high dose CGCA for magnetic resonance angiography (MRA) has allowed improved imaging especially in patients with renal failure. MRA routinely uses 2-3 times the dose of GCCA than the one used for a standard MRI. There have currently been up to 335 cases of NSF that have been tracked by the Yale Center for NSF[19] and over 500 cases have been reported to the FDA. Kreftin noted 1,381 cumulative domestic reports of NSF in association with GBCA's as of April 2010[19a]. There are also a significant number of unreported cases including the ones of this review. NSF was only recognized after large numbers of patients were given GCCA .It was estimated than more than 30 million doses of gadodiamide (Omniscan®) have been given worldwide since its introduction in 1993.[20] Recently, Stinson noted 438 Global NSF reports associated with 47 million administrations of Ommiscan.®[19b]

Previously it was a widely accepted practice to use GCCA in patients with renal failure to avoid iodinated (X-ray) contrast agents.[15,19,21,22] The cumulative doses of GCCA, the combination of rapidly infused, higher than approved doses of GCCA and the clustering of cases in patients with renal failure led to the recognition of this disorder. Evidence of a link between GCCA and NSF was first reported by Grobner and Markman et al.[10,11] Later Thomsen et al reported that more than 90% of proven NSF cases were related to prior exposure to GGCA gadodiamide (Omniscan®) and some to gadopentetate (Magnevist®).[15]

NSF is diagnosed with equal frequency in both sexes and may affect patients of all ages and ethnicities. At the Yale NSF registry about *79% are in Dialysis* (Hemodialysis 52%, Peritoneal Dialysis 16%, ESRD 11%) *17% are non dialysis* (Acute Kidney Injury 10%, CKD Stage IV 1.5%, CKD Stage V 3%) and *post transplant 3%*.[19] There are extremely rare case reports of biopsy-proven NSF in patients with normal renal function. Moreover, only two cases of NSF have been noted after exposure to a macrocyclic.[19c]

Not everyone that is exposed to GCCA develops NSF, but since NSF is a progressive, disabling, non treatable disorder it is advisable to avoid GGCA in patients at risk. Deo et al estimated a risk of 4.3 cases/1000 patient-years in a cohort of 467 American dialysis patients. The risk of NSF after GCCA was calculated to be 2.4%.[23] A European study found NSF in 18% of 102 patients with stage 5 chronic kidney disease with and without dialysis after exposure to gadodiamide.[24] Wertman et al calculated the benchmark incidence of NSF from the data of 4 large US health care centers. The incidence ranged from 1 of 2131 to 1 in 65000 patients, and confirmed previous findings that patients with stage 4 or 5 Chronic Kidney Disease may develop NSF.[25] Accordingly, GCCA and specifically gadodiamide should be avoided in patients with acute renal failure, hepato-renal failure, patients with end stage renal disease, or patients receiving dialysis.[19-25]

Since NSF is a rare disorder there is a multidisciplinary international collaborative effort to study NSF, and there are annual scientific symposiums and a registry available at the Yale University website: http://www.icnsfr.org.[19] The FDA also urges reporting of cases via the Medwatch program by phone 1-800 FDA-1088 or fax 1-800-FDA-0178. The Global Fibrosis Foundation GFF website assist families and patients affected with NSF.

3. Stages of Chronic Kidney Disease

Chronic Kidney Disease (CKD) is defined as either kidney damage or a glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 for more than three months. The National Kidney Foundation defines kidney damage as pathologic renal abnormalities or presence of abnormal renal markers including abnormalities in blood or urine tests or imaging studies and is classified in 5 stages according to the GFR.[26]

Stage 1 CKD is diagnosed as kidney damage with *normal or increased* GFR, more than 90 ml/min/1.73 m^2
Stage 2 CKD is diagnosed as kidney damage with *mild decrease* GFR of 60 to 89 ml/min/1.73 m^2.
Stage 3 CKD is defined as *moderate decrease* of GFR of 30 to 59 ml/min/1.73 m^2.
Stage 4 CKD is defined as *severe decrease* of GFR of 15 to 29 ml/min/1.73 m^2.
Stage 5 CKD is defined as *established kidney failure* with a GFR of less than ml/min/1.73 m^2, or. dialysis

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The corresponding International Classification of Diseases 9 (ICD9) codes for the 5 CKD stages are 585.1, through 585.5. The last decimal point corresponds to the CKD stage and there is also a specific ICD9 code for patient on chronic dialysis, i.e. 585.6 or CKD6.

Currently most laboratories report an estimated GFR and if this is not available it can be obtained via several hand held devices or internet sites such as: www.nephron.com. A serum creatinine alone is not a good estimate of GFR. It also requires knowledge of age, sex and race. Adjustments need also to be taken into account for the presence or absence of proteinuria to estimate risk.[27,28] In passing, it should also be noted that the GRF tends to decrease gradually after age 40, approximately 1 ml/min/1.73 m^2/year. Ideally the kidney function should be stable at the time of staging and can not be used in an acute evolving situation. The estimated GFR obtained with the MDRD formula has other limitations not reviewed here that are beyond the scope of this review.[26,28]

4. Overview of Gadolinium, Chelates, Transmetallation and FDA Warnings

Gadolinium (Gd) is rare earth lanthanide, atomic number 64, one of the transition elements of the Periodic Table, which include manganese, iron, copper and gadolinium. The most common MRI contrast agents are based on paramagnetic compounds that can shorten the longitudinal (T1) and transverse (T2) relaxation of water protons and increase signal intensity, by altering the local magnetic environment. MRI is based on the magnetization properties of atomic nuclei. Gd has the strongest effects on T1 relaxation time because it has seven unpaired electron.[15,20,21,30] The GCCA are FDA-approved intravenous agents used with MRI or MRA to help detect abnormalities of blood vessels, organs and other tissues. There are eight GCCA's currently approved by the FDA in the United States (See Table 1)

Unbound Gd, in its ionic form (Gd^{3+}) is relatively insoluble in water and highly toxic in vivo. Free Gd may provoke liver necrosis as it interferes with enzymatic and cell membranes processes competing with calcium ion passage through muscle cells. Gd is typically bound to a chelate to decrease its toxicity. Furthermore Gd can form precipitates with anions that tend to accumulate in patients with renal failure and has led to the hypothesis that excess exposure to Gd in patients with CKD 4-6 leads to tissue deposition and tissue damage.[29,30,40]

Chelates or ligands are organic molecules that form stable complexes with Gd[15,20,21,29] which enables Gd use in humans. Thus, the chelation of Gd to non toxic ligands allows the formation of a metabolically inert, non toxic complex, which can be given safely in a chelated form that prevents the ion form being dissociated. These chelates have different physicochemical characteristics and stabilities.

The chelates can be ionic or non ionic (the latter are less stable) and linear or cyclical. In the US the only two cyclic GCCA's approved are ProHance® and recently Gadovist® but in Europe they also have Dotarem.®[11] The FDA has also approved Ablavar® Eovist.® and Gadovist.® Ablavar® was approved to evaluate aorto iliac occlusive disease in adults, Eovist® to detect and characterize liver lesions in adults with known or suspected focal liver disease and Gadovist® to detect abnormalities of the blood brain barrier, brain blood supply and circulation. The relative risk for NSF for these agents is noted in the table and has not been reported in peer-reviewed journals.[21]

The *majority of reported cases of NSF have been in patients who received gadodiamide* (Omniscan®)a non ionic, linear agent.[15-19] Not all GCCA pose the same NSF risk[29-37] and the majority are eliminated by the kidney virtually unchanged, except for Gadoxetate that is about 50% eliminated in bile. Therefore, if a patient has renal insufficiency

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TABLE 1 FDA Approved GCCA's in USA*

Brand Name ®	Chemical Name	Chemical Structure	Charge	Protein Binding	Elimination Pathway	Dissociation half-life at pH 1.0	Relative NSF Risk
Omniscan	Gadodiamide	Linear	Nonionic	None	Renal	35 seconds	Highest
Optimark	Gadoversetamide	Linear	Nonionic	None	Renal	Not Available	Moderate
Magnevist	Gadopentetic acid	Linear	Ionic	None	Renal	10 minutes	Medium
MultiHance	Gadobenic acid	Linear	Ionic	≤ 5%	97% Renal	Not Available	Low
Ablavar	Gadofosveset	Linear	Ionic	≥ 85%	91% Renal 9%Bile	Not Available	Lower
Eovist	Gadoxetate	Linear	Ionic	≤ 15%	50% Renal 50% Bile	Not Available	Lower
ProHance	Gadoteridol	Cyclic	Nonionic	None	Renal	3 hours	Lower
Gadovist	Gadobutrol	Cyclic	Nonionic	None	Renal	24 hours	Lower
Dotarem**	Gadoterate	Cyclic	Ionic	None	Renal	> 1 month	Lowest

*. Adapted and modified from references[15,19,19a,,19b,21,40,] The first eight GCCA are approved in the USA *** *Dotaren is available in Europe but is not approved in USA*

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there is an increased risk of having higher Gd levels post exposure to GCCA. The half life of Gd is 1.3 hours in healthy volunteers, 19 hrs with GFR of 20-40 ml/min and 34 hours in patients with CKD5. The half life in patient undergoing peritoneal dialysis is prolonged.[3,19,29,42,43]

The Gd chelates with a linear molecular structure, such as gadodiamide, have the lowest thermodynamic stability and has been found to be up to 100 million times less stable than the most stable cyclic agents.[31] The latter have been rarely associated with NSF.[12,15,19C,21,22,30]

Transmetallation is a process that occurs in biological systems and refers to the replacement of the metal ion in a chelate by another ion. The GGCA complexes dissociates from its chelate or ligands. There is a displacement of Gd^{3+} from the chelating agent. The latter binds endogenous metals (zinc, copper or iron) and Gd in turns binds to endogenous substances (phosphate, citrate, hydroxide or carbonate). Gd can trigger an immunologic reaction leading to fibrosis. This process occurs with endothelial dysfunction and is aggravated by several risk factors (vide infra). Gadodiamide has low stability and is prone to spontaneous dissociation and transmetallation with endogenous ions, leading to the release of Gd^{3+} which may migrate and deposit in tissues and initiate a fibrosis cycle.[29,39,40] Gadodiamide undergoes more transmetallation than other GCCA's and caused the highest increase of urinary zinc followed by gadopentetic acid. The cyclic chelates are insensitive to transmetallation by zinc ions.[15,40] It follows that the safest GCCA is the one that dissociates the least and transmetallation is more likely to occur with linear chelates and the longer the chelate remains in a biological system, a situation that occurs frequently in patients with renal impairment.[15-21]

Over the past few years it has become apparent that the stability of the chelate and the potential release of gadolinium could be a trigger for NSF.[20,22,29,30,40] The pharmacokinetics of Gd differ markedly in patients with or without renal failure. When a GGCA is injected in humans they distribute rapidly into the extracellular space and quickly equilibrate between the plasma and interstitial compartments. The GCCA's are not protein bound, do not undergo biotransformation, have a small volume of distribution and are eliminated unchanged by the kidney. In normal individuals the half life is approximately 1.3 to 1.6 hours and more than 95% of the injected dose is eliminated within 24 hours. Certain GCCA's have a component of hepatic clearance, especially Eovist ® (about 50%) and Ablavar® (about 9%) [15,20,21,29-37]

Gd deposition has been noted in some patients with renal failure and NSF where Gd may have a tissue residence of 4 to 11 months. One of these agents particularly is a non ionic linear chelate: gadodiamide (Omniscan®) has been frequently associated with NSF. It may also be provoked by an ionic linear chelate: gadopentetate (Magnevist®) and infrequently with non-ionic cyclic chelates (Prohance®) and ionic cyclic chelates: gadobutrol (Gadovist®) and gadoterate meglumine (Dotarem®)).The latter is not available in the US. Thereby, current recommendations include specifically avoiding the use of all non ionic linear chelates, especially gadodiadamide (Omniscan®) in patients at high risk.[3,15,20,25-29]

Currently all GCCA carry a new warning about the risk of NSF. The FDA ordered Black Box warnings in 2007 for all GCCA, not just for gadodiamide, and also the CDC performed a safety review of GCCA and found that three of the GCCA: Magnevist®, Omniscan® and Optimark® are associated with a greater risk of NSF and are inappropriate for use among patients with acute renal failure or chronic severe kidney disease with estimated GFR below 30ml/min, unless the diagnostic information is essential an not available with other imaging techniques[32,33] The American College of Radiology[34] has a guidance document for the safe use of GCCA and the European Medicine Agency (EMEA) has also contraindicated gadodiamide and gadopentetate dimeglumine use in patients with CKD4 thru CKD6 and in patients with impaired renal function who have or are awaiting a liver transplant[35]

Renal function tests and GFR should always be determined before administering GCCA and ascertain whether the diagnostic information can be obtained with non GGCA contrast studies or alternate radiological studies (ultrasound, low dose contrast enhanced computed tomography or nuclear medicine studies). If GCCA are clinically indicated the patient and physician should be informed of potential risk of NSF.

5. Clinical Manifestations:

NSF may present with a range of clinical findings (See Table 2) in patients with CKD4-CKD6 or patients with acute renal failure post exposure to GCCA that can become evident weeks to years post exposure to GCCA as shown in the cases reported above and in the current literature.[1-9,15,19,30,36,37]

NSF presents in most cases as a dermatological disorder characterized by thickening and hardening (fibrosis) of the skin, subcutaneous tissues and underlying muscles. NSF has distinctive clinical and histopathological findings.[1-4,6-8,19] The cutaneous changes typically involve the lower extremities, sometimes the upper extremities and less frequently the thorax. The pattern of cutaneous involvement and skin changes are well described by Mendoza et al.[2] and in S. E. Cowper's website.[19] The NSF lesions may evolve into poorly demarcated plaques that range from erythematous to hyperpigmented. NSF spares the face and lacks markers of other similar disorders such as scleroderma. NSF is associated with significant morbidity, debility and mortality. NSF may affect other internal organs including the muscles, fascia, lung, heart and CNS structures and is lethal in a subset of patients.[1-9,36] The relationship between exposures to GCCA, time on dialysis to diagnosis can vary from weeks to years and NSF is frequently *underdiagnosed* by clinicians and pathologists unfamiliar with this disorder.

Initially the dermatological manifestations may include a development of symmetric, bilateral fibrotic indurated erythematous macules, papules and plaques that can result in hyperpigmentation, pink to purple brown discoloration (Image A). The lesions may show non pitting edema, erythema and hardening of the skin and gradual joint contractures. Usually the lesions first develop on the distal limbs (ankles, lower legs, feet and hands) and may move proximally to involve thighs, forearms and trunk[1-9,19] Later there is a progressive expansion, fibrosis and eventual flexion contractures in late stages (Image B). There is increased deposition of collagen and is associated with CD-34 positive fibrocytes (vide infra, see diagnosis).

The severity and clinical features of NSF can vary and most patients have moderate to severe renal insufficiency (CKD4 through CKD6). Cowper has proposed *four major NSF criteria* (patterned plaques, joint contractures, cobblestoning and marked induration / peau d'orange and *five minor NSF criteria* (linear banding, dermal papules, scleral plaques, superficial plaques or patches, macules that

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coalesce in patches or plaques)[19] See Table 2 for range of clinical findings reported in the NSF literature.

Table 2: NSF Symptoms and Signs[2-9,19,37]

Swollen toes, ankles fingers and hands
Scaling, hardening, tightening, tethering, or hyperpigmentation of the skin.
Sclerodactyly and involvement of the dorsum of the hand
Burning pain of extremities and pruritus
Red to violaceous or dark thick "ameboid"advancing patches on the skin
Leathery, cobble stone, "peau d' orange" texture,
Neovascularized scar at site of minor dermal injury
Wooden or doughy or shiny skin
Eye discoloration, scleral plaques
Yellow spots on the whites of the eyes
Loss of joint flexibility.
Joint and bone pains, stiffness and flexion contractures
Loss of walking ability, wheelchair requirement
Neuromuscular involvement with muscle weakness
Deconditioning
Cachexia
Difficulty breathing and reduced lung function
Hypoxia and respiratory failure
Refractory hypotension.

6. Risk factors and NSF Mnemonic:

NSF does not develop in all patients at risk that have been exposed to GCCA. About 3% of patients with stages 4-6 CKD may develop NSF post exposure to GCCA's. The true incidence is difficult to ascertain and it may take weeks to years to develop the typical clinicopathologic findings. The risk is highest with gadodiamide (Omniscan®)[15,19-25,29-37] There are other co-factors including erythropoietin therapy, because of its fibrogenic potential, and the absence of treatment with angiotensin converting enzyme inhibitors which have antifibrogenic properties.[65,66,67] Both can affect the formation of bone marrow derived CD34 fibroblasts which may destabilize the GCCA chelates, predisposing to NSF[2-4,19-25,30-37] The potential risk factors can be remembered with a simple mnemonic I devised *NS FIBROSIS* (Table 3)

Table 3: Risk Factors Mnemonic for NSF

N o treatment with ACE Inhibitors.
S equela of GCCA exposure in patients at risk

F ailed transplant
I mpaired renal function (CKD 4-6 and Acute Renal Failure)
B ig doses of erythropoietin
R ecent vascular injury , thrombosis or surgery
O vercoagulability and metabolic acidosis
S econdary hyperparathyroidism and hyperphosphatemia
I mmunosuppresants and intravenous iron
S ystemic Acute or Chronic Inflammation or Infection

7. PATHOGENESIS:

The pathogenesis of NSF is poorly understood. Most patients with advanced renal failure who are exposed to GCCA's do not develop NSF. The reported risk ranges between 2 to 5%, irrespective of age,sex or race.[3,23] Gd is not the only trigger for NSF.[18] Several triggers and risk factors or co-factors (see Table 3) have been implicated in the development of NSF but *the leading culprit is the use of GCCA in patients with renal disease.* The role of risk factors and whether they can independently initiate the process of NSF without exposure to GCCA's is not clear.[19]

Gd3+ is a trivalent cation that when it is dissociated from a chelate or ligand binds strongly to many tissues. The risk depends on the dose, degree of renal insufficiency and type of GCCA used. There are virtually no cases of NSF in patients with normal renal function[19,29-37]with the exception of a recent poster case presented by Cowper at the 5th Annual NSF Symposium. About 79% of the NSF cases reported to the International Registry at Yale University are in patients who are on dialysis,[19] 10% had had acute kidney failure, 1.5% had CKD stage 4 and 3% CKD Stage 5 and Post-Transplant 3%. The majority of NSF cases are related to prior exposure to gadodiamide (Omniscan®)[15,19-25,29-37] and very rarely NSF is related to macrocyclic compounds.[19c] Gd deposition occurs in humans and has been identified in tissue samples form NSF patients up to 11 months after exposure to gadodiamide.[15,19,36,37,]

It has been proposed that renal failure, metabolic acidosis and endothelial dysfunction increase the half life of Gd which allows chelated Gd to dissociate and to deposit in tissues. Macrophages next phagocytose Gd and produce local profibrotic cytokines that recruit *circulating fibrocytes (CF).* The latter are bone-marrow-derived cells that are normally recruited to sites of tissue injury to aid in wound healing and tissue remodeling.[19]

The CF can be *identified with special markers*. It has a CD34/ procollagen dual positive profile and is blood borne. Under certain conditions and triggers the CF can leave the circulation and differentiate in the dermis into cells very similar to dermal fibroblasts. There may also be an activation of *fibrogenic cytokines* and stimulation of the transforming growth factor *(TGF)-beta-1-pathway* which leads to activation of dendritic cells and generation of a vicious cycle of TGF-beta-1 generation and further recruitment of antigen presenting dendritic cells and activation of CF with eventual tissue fibrosis.[2,10-25,29-34,37]

Image B

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