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

Nephrogenic Systemic Fibrosis: Why Should We Be Concerned? Part 2

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

Nephrogenic Systemic Fibrosis (NSF) is a rare clinico-pathologic disorder characterized by thickening and hardening of the skin and underlying tissues. NSF may affect 2-5% of patients with chronic kidney disease (CKD) stages 4-6 or acute renal failure patients after exposure to gadolinium containing contrast agents (GCCA). On September 9, 2010, the FDA issued new warnings requiring that GCCA carry a warning label about NSF risk and contraindicated the use of Magnevist,® Omniscan,® and Optimark® in patients with CKD stages 4-6 or acute kidney injury/failure. These topics were reviewed in the previous issue.[68] The second part of this review emphasizes NSF diagnosis; differential diagnosis; prognosis; prevention; treatment; the good, the bad, and the ugly of NSF; and provides a concluding summary.

8. DIAGNOSIS
A diagnosis of NSF requires integration of patient history, clinical presentation, physical exam, and biopsy findings. Most cases of NSF appear weeks to months or years after GCCA exposure. The epidermis is usually not affected. Thus, a deep skin incisional or punch biopsy is required for diagnosis since NSF may be missed, and NSF frequently extends beyond the subcutaneous tissue. It is important to obtain a deep tissue biopsy that includes subcutaneous fat, fascia, and even muscle. The biopsy should be evaluated by an experienced dermatopathologist.[15] Currently, no specific laboratory test exists for NSF. Repeat review of a biopsy or a repeat biopsy may be needed if the initial biopsy is non-diagnostic but the clinical presentation is suggestive of NSF.[1-24] The patient should also be asked if they have had prior renal disease and it should be specifically inquired whether an MRI or MRA procedure was performed with intravenous GCCA.[15,19,28-37]

Light microscopy findings may range from elusive proliferation of spindle shaped dermal fibrocytes to marked thickening of the dermis with collagen bundles separated by numerous clefts and tram tracks. There is proliferation of dermal fibroblast and dendritic cells and the entire dermis is eventually involved. There is also a focal increase in dermal mucin and elastic fibers with minimal or absent inflammation. Sclerotic bodies, also known as ellastocollagenous balls, have been reported in patients with NSF.[19d] At the Fourth Annual NSF symposium at Yale University in 2010, Cowper described a NSF scoring system based on clinical and pathologic findings. When present, each of the following four biopsy findings is ascribed 1+: increased cellularity, tram tracks, thick and thin collagen fibers, and septal invasion. The lollipop sign, when detected, is assigned 3+. When these findings are added up, a score of 4+ or more is highly consistent with a diagnosis of NSF. A score of 3+ is also consistent with NSF. A score of 2 is suggestive of NSF, but a score of 1+ is inconsistent with NSF.[19]

Trichrome stain may show prominent accumulation of fibrotic tissue in the interfascicular septae and surrounding muscle fibers. Immunohistochemical studies show dual positive CD34 and procollagen-1 dermal cells, which are thought to be circulating fibrocytes that have been recruited to the dermis. There is also an increase of CD68+ and factor XIII+ dendritic cells.[1-4,19,36,37,45] The diagnosis rests on good clinical, pathologic correlation and exclusion of other disorders.

9. DIFFERENTIAL DIAGNOSIS:
A history of acute renal failure or CKD stages 4-6 associated with the skin or systemic changes noted above, plus a prior history of intravenous GCCA, is highly suggestive of NSF. The differential diagnosis is quite broad, and includes other fibrosing skin disorders that can be excluded by clinical, laboratory, immunologic, or histopathologic studies.[1-37] NSF is a diagnosis of exclusion and may appear months to years after exposure to GCCA. All clinicians and especially nephrologists should maintain a high index of diagnostic suspicion when atypical skin lesions or previously noted clinical features[68] appear in CKD patients who are on maintenance dialysis and have been previously exposed to GCCA The following disorders should be considered:

Progressive Systemic Sclerosis or *Scleroderma* may mimic NSF, but usually Raynaud's phenomenon is present, and antinuclear, anticentromere, anti-SCL-70, and/or anti-DNA topoisomerase antibodies are positive. Clinically important is the presence of face involvement, which is absent in NSF.[1-9,36,37,40,45] This diagnosis can also be excluded taking into account the criterion suggested by the American College of Rheumatology of presence of one major criterion (symmetric sclerosis proximal to the metacarpal or metatarsal phalangeal joints) or two minor criteria (digital pitting scars, loss of substance from the finger pad, sclerodactyly, or bibasilar pulmonary fibrosis).

Pretibial Myxedema in Basedow's disease or hypothyroidism can be excluded by clinical and thyroid studies. There is a local deposition of hyaluronic acid in the dermis and subcutaneous

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tissues. It can also be excluded by the absence of exposure to GCCA and the presence of renal insufficiency, which is usually present in NSF.

Erythema Nodosum has multiple etiologies including drug-induced. Most lesions associated with infections heal within two months, but may persist up to four and half months. In contrast, the idiopathic erythema nodosum may last more than six months. The lesions may appear as red, tender nodules measuring up to five centimeters in diameter and are found on the anterior surface of the lower legs, ankles, calves, thighs, and arms. In patients with inflammatory bowel disease, attacks correlate with bowel activity. Other clinical features of NSF noted previously in Tables 2 and 3 are not present.[68]

Pyoderma gangrenosum can be excluded by the findings of an ulcerative cutaneous lesion in patients that may have underlying ulcerative colitis, Crohn's diseases, polyarthritis, or leukemias.

Scleromyxedema typically has a different distribution pattern that includes the face and neck, and is frequently associated with a monoclonal gammopathy, usually with an IgG lambda paraprotein, which is absent in NSF. In NSF, serum protein electrophoresis and immunoelectrophoresis studies are negative.[1-7,40,45]

Eosinophilic Fasciitis does not involve hands and feet; whereas, these are involved in NSF. Pathologic eosinophilia, eosinophilic tissue infiltration, and hypergammaglobulinemia are present, all of which are absent in NSF.[2-5,40,45]

Sclerodermatous chronic graft versus host disease is usually distinguished by an antecedent allogeneic stem cell bone marrow transplant and other clinical features.[9,40,45]

Granuloma Annulare may present with raised, reddish, flesh-colored bumps, forming a ring pattern on the feet and hands. These patients usually do not have CKD stages 5-6, nor have they been exposed to GCCAs.[2-4]

Calciphylaxis is usually noted in patients with CKD stages 5-6. It may be associated with NSF, but it is distinguished by the typically tender violaceous, purpuric skin lesions and deranged mineral metabolism. The classical findings on the physical exam include central necrosis of the skin lesions, plus changes of ischemic necrosis in the skin biopsy, due to increased vascular calcification that are much different from that noted in NSF.[2-4,36,37,45]

Lipodermatosclerosis is usually noted in women over 40 years of age and affects the area above the malleolus in patients with long standing venous insufficiency and edema. Involvement above the knee is rare. It may induce a panniculitis that heals with sclerosis and hyperpigmentation due to hemosiderin deposition.[2-4,19,36,37,40]

Benign Nodular Metastatic Calcifications can occur in patients with CKD stages 5-6 and is caused by precipitation of calcium and phosphate salts that may accumulate in the skin, subcutaneous tissues, and periarticular locations. These lesions can be detected with simple X-rays and are different from those noted in NSF[2-9,36,37,45]

Necrobiosis Lipoidica Diabeticorum may appear in diabetic patients and these patients are not necessarily on dialysis or have a history of exposure to GCCA. It typically presents with leg plaques that are red along the edge and gold in the center

Lichen Planus may appear as reddish-purple, flat or itchy bumps. It may appear in the wrists, ankles, low back, neck, legs, and genitals.[2-4,19,36,45]

Psoriasis presents with raised plaques covered with silvery scales. It may affect the scalp, low back, elbows, and knees, which are different locations from the lesions noted in NSF.

Amyloidosis can be differentiated by Congo red staining of affected organs (kidneys, anterior abdominal adipose tissues, and rectum) and lack of exposure to GCCA. $Beta_2$-microglobulin amyloidosis occurs in patients with CKD stage 6. Flexion contractures from amyloidal infiltration and adherence of the flexor tendons may provoke prominent subcutaneous tissue masses on their palms, which is atypical for NSF.[4,45]

10. PROGNOSIS:

NSF is a chronic, progressive, and debilitating illness that is associated with increased morbidity and mortality. It progresses over the years, but in a few cases, the early skin changes may improve with normalization of renal function or with a kidney transplant.[2-4,19,36,37] NSF can be disabling, debilitating, and results in falls and fractures. Among patients with CKD stages 5-6, those with cutaneous changes of NSF have a threefold increase in mortality within 2 years of diagnosis, mostly due to cardiovascular and pulmonary events. About 5% of NSF patients have a rapid and progressively fulminant disease that may contribute to death by restricting mobility and ventilation.[2-6,19,29-37]

The natural history of NSF is not fully known, but about one third of affected patients die of NSF complications, one third of NSF patients have no improvement whatsoever, and the remainder have modest improvement, especially if the renal function recovers from an acute episode or if the patient has a renal transplant.[2-4,19]

11. PREVENTION:

The great majority of NSF cases have been noted following exposure to GGCA, especially after administration of gadodiamide and magnevist.[15,19,36,37] Thus, the best preventive measure is avoidance of GCCAs in patients with acute renal failure, chronic renal failure (stages 4-6) with GFR of less than 30 ml/min/m^2, hepatorenal syndrome, and in the immediate post transplant period. Ideally, other alternatives should be considered that do not require GCCAs, such as ultrasonography, CT scan, nuclear medicine, or non-enhanced MRA. MRA with GCCA should be avoided in patients with NSF.[19]

If GCCA use is necessary, avoid GCCA during inflammatory or post-surgical events. Clinicians and particularly radiologists should always use the lowest dose and the most stable macrocyclic chelates or low dose high relaxivity GCCA. Preferably, avoid using linear non-ionic chelates and repeated examinations with GCCAs. The patient should sign an informed consent form and should be informed of the benefits of the study, the risks of NSF, and alternatives.[13-25,29-37]

Hemodialysis given immediately (1 to 4.5 hours) after administra-

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tion of GCCA increased the elimination of gadodiamide by 73%, 93%, and 99%, with one, two, and three treatments, respectively.[3,15,19,36-40] There is no evidence that immediate hemodialysis can prevent NSF. Ideally, a functioning angioaccess should be available prior to the exposure to GCCA in patients with CKD stages 4-6, but there is no consensus that this regimen is always effective.[15] The FDA and the American College of Radiology suggest prompt hemodialysis, no later than 2 hours after GCCA exposure.[32-36] However, the role of hemodialysis in NSF prevention remains uncertain.

12. TREATMENT:
There is no specific or established therapy for NSF other than recovery of renal function.[13,4,12,19,45-47] Currently, no single treatment has been shown to be effective, but physical therapy and swimming may slow down NSF progression and prevent incidence of joint contractures.[4,19] Various attempted regimens include:

Steroids such as oral prednisone in doses of 1 mg/kg po daily may affect the renal or cutaneous disease and have some effects in a subset of patients. Intralesional or topical corticosteroids under occlusion calcipotriene (Dovonex®) and clobetasol (Temovate®) have been tried with limited benefit.[3,12,19]

Immunosuppressive therapies including cytoxan or cyclosporine have shown no benefit,[2,4,12,19,37] but recently sirolimus (Rapamune®) has been reported to be of benefit.[41]

Thalidomide, an inhibitor of angiogenesis, at doses of 50-100 mg daily (given with proper precautions) may improve early cutaneous changes, but is ineffective in patients with NSF of longer duration.[44]

Trental® (pentoxifylline) acts by blocking TGF, has antifibrotic activity associated with tumor necrosis factor alpha (TNF-α) antagonism, and at doses of 400 mg po TID may slow or arrest the skin changes.[10,45]

Gleevec® (Imatinib mesylate) 400 mg daily acts by inhibiting c-Abi kinase and the tyrosine kinase activity of PDGF receptors and is reported to improve joint mobility and skin tethering, but may provoke fluid retention and gastrointestinal upset.[45-47]

IVIG intravenous immunoglobulin in high doses (0.4 gm/kg daily for 5 days each month) may modulate the immune response and cytokine and lymphocyte production, and has been used in England.[48]

Sodium Thiosulfate 12.5 to 25 gms IV thrice weekly at the end of hemodialysis provided an improvement of skin discoloration, pain, and joint stiffness, but there was no major improvement in late stages of NSF.[49-51]

Extracorporeal Photopheresis or Photochemotherapy involves exposure and reinfusion of blood monocytes to photoactivated 8-methoxypsoralen. This induces monocyte derived TNF-α, which in turn suppresses collagen synthesis, and led to improvement in skin tightness and ambulation, but in other cases only limited effects were noted.[40,52-56]

Ultraviolet A phototherapy (UVA) inhibits procollagen synthesis in human skin, but has provided inconsistent results and may not penetrate to the dermis. UVA is often used with other therapies.[40,57-59]

Plasmapheresis (one to three, five day courses) contributes to immune modulation and has been reported to be of benefit in some cases, but in others, no benefit was detected.[40,60-61] A trial is currently underway at Loma Linda University and is recruiting participants.

Kidney transplantation may offer the best hope for NSF, but it is not always widely available and its efficacy is unproven.[40,62,63]

13. The Good, the Bad, and the Ugly of NSF.
In 2006, the link between NSF and GCCA was established.[10,11] The good news is that the prevalence of NSF has been decreasing since 2007, due to a decrease in the use of gadodiamide and after adoption of GCCA restrictive guidelines imposed by the FDA.[32-37] The bad news is that once NSF is diagnosed, it tends to be a progressive and disabling disorder, and there are very few effective choices of therapy available. The ugly news is that personal injury lawyers are already involved recruiting patients with NSF via the internet to initiate claims and lawsuits. Physicians can avoid these headaches by not using GCCA in at risk renal patients.

14. Summary:
NSF is a rare, fibrosing, systemic disorder that affects the connective tissues of patients with chronic kidney disease stages 4-6 and/or acute renal failure post exposure to GCCA. The NSF skin lesions appear predominantly on the extremities and may include plaques and papules with or without pigmentary changes. A diagnostic deep skin biopsy shows an increased number of dermal fibrocytes and altered pattern of collagen bundles with interspersed increased focal mucin deposits. There is no specific treatment for NSF and the best therapeutic strategy for healthcare professionals is to avoid exposure to GCCA, especially gadodiamide (Omniscan®) in renal patients at risk.

The reason why we all should be concerned about NSF is that we are most likely seeing the tip of the iceberg. NSF can lead to serious complications and death. NSF is potentially preventable if we avoid using GCCA in at risk renal patients.

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RETRACTION

El Paso Physician magazine Volume 35 Number 5. Article "Nephrogenic Systemic Fibrosis: Why Should We Be Concerned? Part 1", on page 8 it should read **Stage 5 CKD** is defined as established kidney failure with a GFR of less than 15 ml/min/1.73 m2 , or dialysys (Somehow **15** was dropped).