Review Article

Nephrogenic systemic fibrosis: A review of the new conundrum

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ABSTRACT

Nephrogenic systemic fibrosis is an idiopathic, sclerosing condition that occurs only in patients who have impaired renal function. Although its most conspicuous manifestation is in the skin, the condition involves multiple organ systems and is potentially fatal. Its postulated association with gadolinium-based magnetic resonance contrast agents has attracted attention. The distinctive clinical features of this entity include a prodromal systemic inflammatory syndrome followed by a chronic course of fibrosis that has a predilection for the skin and subcutaneous tissues of the extremities. The progressive systemic fibrosing process involves multiple organs and contributes to the morbidity and the increased mortality. Appropriate preventive action, prompt recognition and timely reporting of cases may enable better management of this condition.

Natl Med J India 2009;22:302–6

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is an idiopathic, potentially fatal, multi-system sclerosing disorder found exclusively in patients with impaired renal function. The original case definition of NSF included patients with dermatological manifestations, such as areas of hardened skin with slightly raised plaques or papules, with or without pigmentary alteration, and with biopsies showing characteristic pathological changes.[1] However, it was soon realized that manifestations of NSF, although most conspicuous in the skin, involve many other organ systems. Aptly, the original term for this disease, nephrogenic systemic dermopathy, was changed to NSF. Notwithstanding its debilitating potential, NSF is relatively rare with <300 cases having been reported over the past 10 years to the US Food and Drug Administration (FDA) and to the NSF registry at Yale University.[1,2] Yet, NSF has attracted widespread attention primarily because of the recently postulated association of gadolinium-based magnetic resonance (MR) contrast agents (GBCAs) in the pathogenesis of NSF. Other features, such as multidisciplinary character of NSF, the large population at-risk, the intriguing nature of its proposed pathogenesis, and the lack of a consistently effective therapy have also caught the attention of the medical profession. We summarize the distinct features of this enigmatic disease, as well as the hypothesized aetiological mechanisms, with particular emphasis on the association of NSF with GBCAs.

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A BRIEF HISTORY

Although recognized in 1997 in California, NSF was first described by Cowper *et al.* in 2000 as a cutaneous scleromyxoedema-like disorder in patients with end-stage renal disease (ESRD).[3] In the single case series that has been reported to date from India, Panda *et al*. described the occurrence of NSF in 6 patients among a cohort of 2146 patients with chronic kidney disease (CKD) on dialysis. However, these patients were not investigated for a history of exposure to GBCAs.[4] In January 2006, a possible causal link between NSF and a GBCA, gadodiamide (Omniscan) was first proposed by Grobner on the basis of his observations in 5 patients with ESRD.[5] Until then, GBCAs had a remarkable safety record with gadodiamide alone having been administered to more than 30 million patients since its introduction for clinical use in 1993, with no important adverse events.[6] In 2006, Marckmann *et al.* suggested that gadodiamide was a putative causative agent for NSF in 13 patients with CKD who had undergone MRI with gadodiamide prior to the development of NSF.[7] Subsequently, there was a steady increase in the NSF case reports and case series that further supported the temporal and causal association of GBCAs and NSF. Interestingly, most of these reports mentioned 3 of the numerous commercially available GBCAs, namely gadodiamide, gadopentetate dimeglumine (Magnevist) and gadoversetamide (OptiMARK). In those cases in which a specific agent could be identified, the gadolinium agent most frequently implicated (>90% of cases) was gadodiamide.[8] The exact reason for the predominant association with gadodiamide alone is not yet clear but factors that might be involved are discussed later. Nevertheless, the reports of a large number of cases over a relatively short period of time prompted the US FDA to issue an alert to healthcare providers on GBCAs and their possible role in the causation of NSF in June 2006; a public health advisory was similarly alerted in December 2006. In May 2007, the US FDA requested manufacturers of the 5 GBCAs used in the USA for MRI (gadodiamide, gadopentetate dimeglumine, gadoversetamide, gadobenate dimeglumine and gadoteridol) to include a 'black box' warning on the product labels highlighting the risk they posed to patients with renal impairment (*http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108919.htm*). The US FDA also set up a reporting programme so that healthcare providers could report instances of NSF caused by

GBCAs.[2] To date, the link between NSF and GBCAs continues to be an issue of intense discussion among all concerned parties.

EPIDEMIOLOGICAL CONSIDERATIONS

The precise epidemiological profile of NSF is not yet apparent as most cases of NSF have occurred in clusters. Nevertheless, some information can be gleaned from the available data. The estimated incidence of NSF in patients with CKD (glomerular filtration rate [GFR] <30 ml/minute/1.73 m^2) exposed to GBCAs is 4.3 cases per 1000 patient-years.[9] The reported odds ratio for acquiring the disease after gadodiamide exposure is 32.5 (95% confidence interval [CI] 1.9–549.2; p<0.0001).[7] The age range at onset varies from 8 to 87 years with the mean age being 46.4 years.[10] There is no age, gender, race, ethnic group or geographic predilection. However, there is reason to believe that the actual incidence may be higher, in view of our limited current understanding of this entity, the non-recognition of the subclinical and atypical forms of the disease that may only be apparent on a deep skin biopsy, and under-reporting because of a lack of awareness.[11,12] Further, the 24-month mortality rates after GBCA exposure have been found to be 48% in patients with cutaneous changes and 20% in patients without them (adjusted hazard ratio 2.9; 95% CI: 1.4–5.9).[13]

RISK FACTORS

The exact aetiology of NSF is still under investigation. It occurs in patients with acute or chronic severe renal insufficiency (GFR <30 ml/minute/1.73 m^2), or in patients with renal dysfunction caused by hepatorenal syndrome or in the perioperative liver transplantation period.[2] Thus far, there has not been any report of NSF following GBCA exposure in a patient with normal renal function or mild-to-moderate renal insufficiency. Although the average volume of the gadodiamide administered in the patients reported by Grobner was 35 ml, NSF has been associated with administration of both standard- and high-dose gadolinium.[8] The development of NSF is correlated neither with the duration nor the cause of renal failure.[14]

Further, the knowledge that not all patients with ESRD exposed to GBCAs develop NSF led to a search for other triggers which, alone or in combination, may have a role in the pathogenesis of NSF. The various risk factors that have been implicated are metabolic acidosis, hypercoagulability states, thrombotic events, recent vascular surgery, recent transplant failure, high-dosage erythropoietin (EPO) therapy, elevated parathyroid hormone (PTH), hypothyroidism, antiphospholipid antibodies, and elevated serum iron, calcium and phosphate levels, which might promote transmetallation with gadolinium chelate (vide infra).[11,15–17] These factors are believed to generate a pro-inflammatory milieu by leading to proliferation of cytokines that may predispose patients with ESRD to NSF after exposure to GBCAs. In fact, a 'cumulative risk factor model' has been proposed, which states that patients with a higher risk factor load may need only low doses of GBCAs to trigger NSF and vice versa.[12,15] Although this hypothesis is scientifically tenable the exact manner in which the various risk factors interact, if at all, remains to be worked out. The case for such triggers is strong but convincing evidence is not yet available.

RENAL IMPAIRMENT, NSF AND GBCAs

GBCAs are used extensively for MRI scans because of gadolinium's ability to accentuate the contrast between normal and pathological tissue. GBCAs exist as water-soluble gadolinium-chelate complexes; gadolinium in its free form (Gd^{3+}) can result in a toxic reaction *in vivo*.[6] In normal individuals, GBCAs are almost exclusively excreted through the kidney with a half-life of approximately 2 hours. The half-life of these agents is prolonged in the presence of deranged renal function.[6] Further, the dissociation of gadolinium ions from its chelate under the influence of endogenous metals, particularly iron or acids—a process referred to as transmetallation—is possible and leads to the release of toxic, free gadolinium ions.[15] In patients with renal failure, the combination of metabolic acidosis,[5] elevated levels of free iron due to a variety of reasons,[15] and the absence of adequate clearance of GBCAs creates a milieu that may favour the release of such injurious ions. Using electron microscopy and X-ray spectroscopy, intracellular and interstitial gadolinium precipitates have been identified in skin biopsy specimens of patients with NSF.[18,19] Presently, not enough evidence exists to state that such deposition is more than an incidental finding. The plausible hypothesis is that these tissue deposits may provoke tissue fibrosis by inciting various mediator cells, such as the circulating fibrocytes (CFs)—cells that were first described in relation to wound repair[20]—and/or by serving as their targets.[15] The reason for the skin being the primary organ of damage in NSF also remains unknown.

Most cases of NSF reported so far have been associated with linear, non-ionic GBCAs (gadodiamide and gadoversetamide) that tend to favour transmetallation and release of free Gd^{3+} by virtue of their chemical structure.[6] The available brands of GBCAs differ from each other in 2 important aspects. First is the chelate, which binds to the gadolinium ion; second, and perhaps more important in this context, is the affinity of this chelate to bind the gadolinium ion and prevent its release as toxic, free gadolinium at physiological pH. Among the US FDA-approved contrast agents, this affinity is lowest for gadodiamide and gadoversetamide by a factor of 100 to 1000 compared with that of gadopentetate dimeglumine, gadobenate dimeglumine and gadoteridol. Gadodiamide and gadoversetamide are also the only contrast agents with a substantial amount of excess chelating agent added to the commercially distributed preparation to minimize the risk of release of free gadolinium (gadodiamide contains less excess chelating agent than gadoversetamide).[8] Paradoxically, the excess chelate has been postulated by some to confer an added risk of transmetallation with endogenous ions.[8,21] However, this view is contested by others.[22]

Thus, the physicochemical properties and stability of GBCAs are likely to be important determinants in the pathogenesis of this condition. The other issues that could be important include the limited use of some GBCAs, difference in the *in vivo* properties of various GBCAs leading to dose variations, under-reporting of NSF, and a lack of patients' complete GBCA exposure history. Thus, the relative risk among various GBCAs is not equal but it is widely believed that NSF could develop potentially after the administration of any GBCA to a patient with ESRD.[8,11] Whereas the mechanism has not yet been ascertained, the epidemiological evidence linking GBCAs to NSF is strong.

CLINICAL FEATURES

The onset of NSF is heralded by a variable systemic inflammatory syndrome (fever, hypotension, subacute swelling of the distal extremities and elevated blood levels of inflammatory markers), which tend to occur immediately after exposure to a GBCA. However, this acute phase may go unrecognized because of the co-morbid illness in patients with ESRD. A chronic phase of fibrosis ensues after an interval that varies with each patient.[15,16] According to the US FDA, the development of NSF after administration of a GBCA can take from 2 days to 18 months.[2] The

typical chronic course consists of generalized oedema associated with severe induration of the skin of the distal parts of the extremities. This may extend to involve the thighs, antebrachium, lower abdomen, dependent parts of the body (such as the pre-sacral area), or high blood-flow areas (such as the skin overlying an arteriovenous dialysis fistula).[12,15,16,23] The skin induration may be aggressive, have a 'woody' consistency, be associated with constant pain, pruritus, a subjective sense of restlessness, and loss of skin flexibility. The primary skin lesions of NSF include symmetric, erythematous papules that coalesce to brawny plaques with an 'amoeboid' or serpiginous edge. The skin can have a peau d'orange appearance. Distinct nodules also can be seen.[10,12,15,16,23,24] Yellow palmar papules resembling cutaneous calcinosis have been reported.[25] The associated early symptoms include sleeplessness and transient, diffuse hair loss.[10] In addition, yellow scleral plaques have been reported in patients with NSF. The most commonly affected areas are the extremities (ankles to thighs and wrists to arms). Trunk involvement is less frequent, and the face and neck are rarely affected. The involved joints usually contract leading to a distinctive physical appearance with the elbows and knees angled inward, causing a restricted range of motion and progressive loss of ambulation that might result in confinement to a wheelchair.[10,25–27] In addition, there is progressive involvement of the muscles, tendons, diaphragm, testes, heart, liver, lungs, pleura, pericardium, and duramater.[12,15,16,28,29] It is the systemic involvement that contributes to the distressing morbidity and the increased mortality in patients of NSF.[13,23] In patients presenting with this clinical picture, a history of exposure to GBCAs should be actively sought and the kidney function should be assessed if risk factors for it are present.

DIAGNOSIS

The characteristic manifestations in an appropriate clinical setting can point towards the diagnosis of NSF. However, the diagnosis is established by doing a deep skin biopsy from the affected areas. The biopsy findings that confirm NSF include dermal spindle cell (fibroblast) proliferation (usually staining positive for CD34 and procollagen) with frequent extension into subcutaneous tissue, presence of dermal mucin, variable infiltration of CD68/XIIIa-positive macrophages, and presence of broad collagen bundles with clefts and fragmented elastin.[15,16,24] Increased expression of TGF-beta1 has also been observed.[30] The CD34 immunostaining profile is actually characteristic of 'circulating fibrocytes', i.e. circulating cells of bone-marrow origin expressing markers of both connective tissue cells and circulating leucocytes. The absence of inflammatory cells is a characteristic finding. Osseous metaplasia, osteoclast-like giant cells and calciphylaxis have been seen in some NSF biopsies.[31] On a technetium^{99m}-diphosphonate scan, areas of increased uptake can be observed in muscles, and conventional X-rays may reveal soft tissue calcification. On MRI, axial T1-weighted and fat-suppressed T2-weighted images show symmetrical thickening of the skin and oedema of the soft tissues.[22] However, imaging studies are not essential to evaluate a patient suspected with NSF.

The important differential diagnoses of NSF include scleroderma, scleromyxoedema, eosinophilic fasciitis, graft-*versus*-host disease (GVHD), eosinophilia–myalgia syndrome, toxic oil syndrome, calciphylaxis and pretibial myxoedema.[15,16] The features that help in differentiating NSF from the other conditions include an absence of facial involvement, circulating paraprotein or serological antibodies, temporal relation to GBCA exposure, characteristic pathological findings in involved tissues and the appropriate clinical context [10,15,16] The manifestations can be wide ranging, may mimic unrelated diseases and over time may vary even in the same patient. Further, the reported occurrence of NSF in the setting of diseases, such as systemic lupus erythaematous[32] may further compound the diagnostic dilemma. Hence, the diagnosis of NSF should be based on both clinical and histopathological features after excluding the related entities. The histopathological picture in the late stages of NSF may be dominated by scarring alone and features characteristic of NSF may not be apparent. In such instances, typical signs and symptoms in the appropriate clinical context may be the only evidence for diagnosing NSF.[24]

PROGNOSIS

Our understanding of the natural history of NSF is incomplete. NSF has been found to increase the morbidity and mortality in affected individuals.[13,33] Excruciating pain or pruritus is a major debilitating component in some patients. If the disorder occurs over a joint, many patients become dependent on a wheelchair within weeks of onset of the disease because of the contractures. Systemic involvement is associated with a more extensive cutaneous disease.[22,25,33] Rapid progression and the extent of cutaneous disease in turn portend a poorer prognosis.[13] Several patients with NSF have died as a result of complications of their kidney disease or transplant surgery. As mentioned above, some patients with NSF (estimated at <5%) have a rapid and fulminant disease that may result in death. NSF *per se* is not the cause of death but may contribute to it by restricting effective ventilation, or restricting mobility to the point of causing an accidental fall that may be further exacerbated by fractures and accompanied complications.[1] Some patients report a gradual improvement in mobility and slight softening of the skin over time. However, unequivocal complete spontaneous healing in a patient with ongoing kidney disease has not yet been reported.

RECOMMENDED ACTIONS

Currently, there is no permanent effective cure for patients who develop NSF. Prompt improvement in renal function, as a result of transplantation or medical therapy in the form of haemodialysis after exposure to GBCAs, seems to accelerate the elimination of gadolinium from the body. However, this has not been shown to prevent NSF.[22] Moreover, obtaining vascular access for the sole purpose of removing GBCA may not always be feasible in non-dialysis CKD and peritoneal dialysis patients as it involves additional risks.[11] Other treatment modalities that have been tried with variable success include steroids, plasmapheresis, extracorporeal photopheresis, intravenous immunoglobulin, ultraviolet light therapy, physical therapy, PUVA (psoralens with ultraviolet A) and pentoxiphylline.[33–38] In the absence of any effective treatment, prevention through vigilant and judicious use of GBCAs seems to be the only possibility. In this regard, the American College of Radiology recommends the following practical approach:[39]

1. No additional precaution for kidney disease patients with stage 1 or 2 CKD (defined as presence of kidney damage with GFR >90 ml/minute/1.73 m^2 or GFR between 60 and 89 ml/minute/1.73 m^2, respectively). However, patients with any level of renal disease should not receive gadodiamide for their contrast-enhanced MR examinations.
2. Checking the renal function of the patient, serum creatinine level, or GFR before accepting a patient for an MR imaging or

angiographic examination is specifically not required. Instead, all requests for MR should be pre-screened with specific emphasis on the presence of a history of kidney disease or dialysis or risk factors for the same. If the disease is present but mild (stage 1 or 2), modification of how the study should be performed (relative to a patient with no renal disease) does not appear to be indicated except for the avoidance of gadodiamide.

The management is more complex in patients with known renal dysfunction (i.e. stages 3, 4 or 5 kidney disease or those with acute kidney injury). Reducing exposure to the contrast agent and/or avoiding agents with proven risk are certainly logical. As such, the question of the use of a GBCA in this group of patients is one of considering the risk of NSF against the benefit of diagnostic information that the contrast-enhanced MRI/MR angiography may provide in a given clinical context.[39] In certain instances, this diagnostic benefit may outweigh the relatively small risk of NSF. In addition, an alternative test such as a contrast-enhanced CT/CT angiography, has an inherent risk of iodinated contrast-induced nephropathy in the same group of patients.[8,40,41] Hence, an individualized approach with discussion of the risk–benefit of GBCA exposure and available alternative radiological modalities between the patient, the involved physicians and the radiologist is obligatory.[16,41]

During contrast-enhanced MR examination, the least dose necessary to complete the study should be used, irrespective of the GBCA employed, and repeat studies may be avoided. Macrocyclic agents (gadoteridol [ProHance], gadobutrol [Gadovist] and gadoterate meglumine [Dotarem]; none are currently available in India) that have not yet been associated with NSF should be preferred.[6,42] Patients with renal insufficiency who receive gadolinium agents should be periodically monitored for symptoms and signs of NSF. In addition, the MRI report of every patient should mention the type, specific brand name, dose, route and rate of administration of the GBCA[39] so that it can facilitate a retrospective investigation whenever required. The clinical report of patients known to be suffering from renal failure, whenever possible, should also mention the GFR at the time of study. The National Kidney Disease Foundation recommends the MDRD (modification of diet in renal disease) study equation to compute the estimated GFR (eGFR). The user-friendly calculator using this equation can be accessed at *http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm*. The only variables required for utilizing this calculator are serum creatinine, age, sex and the gender of the patient. Such estimation may not be accurate in the setting of acute renal failure.[43] If a patient develops NSF despite these measures, it should be documented and notified to the databases that include the US FDAs MedWatch program (*http://www.fda.gov/medwatch/*) and the international NSF registry at Yale University (*http://www.icnfdr.org*).

In conclusion, there is a pressing need to disseminate unambiguous information about NSF to healthcare providers to facilitate appropriate preventive action, prompt recognition, quality research, and timely reporting of cases. This will improve our understanding of the role of GBCAs, renal impairment and other co-morbid conditions in the development of NSF and may enable us to better manage this seemingly iatrogenic condition.

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