Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure

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Abstract

Background. Nephrogenic systemic fibrosis is a debilitating disease occurring exclusively in patients with renal failure. The aetiology of nephrogenic systemic fibrosis is unclear, but recent reports suggest that exposure to gadolinium for enhancement of magnetic resonance imaging may play a role. In the present study, we assessed the association of exposure to gadolinium with the development of nephrogenic systemic fibrosis in patients with various stages of chronic kidney disease.

Methods. We analysed the exposure to gadolinium and development of nephrogenic systemic fibrosis in 849 patients on renal replacement therapy over 5 years. We also performed inquiry of development of the nephrogenic systemic fibrosis in 592 patients exposed to gadolinium and estimated to be in stages 3 and 4 of chronic kidney disease.

Results. In 849 patients undergoing chronic dialysis from 2001 through 2006 time period, four of the 261 who had received gadolinium (1.5%) and none of the 588 not exposed to gadolinium developed clinically apparent disease. The odds ratio for developing nephrogenic systemic fibrosis was 6.671 [95% confidence interval (CI) 1.537–53.97] in patients with a single gadolinium exposure compared to patients without gadolinium exposure. This ratio increased to 44.5 (95% CI 2.362–2913) in patients with multiple gadolinium exposures compared to patients not receiving gadolinium. None of the 592 patients estimated to be in stage 3 or 4 of chronic kidney disease developed nephrogenic systemic fibrosis after exposure to gadolinium.

Conclusion. Gadolinium exposure is associated with nephrogenic systemic fibrosis in patients on chronic renal replacement therapy at a low rate. This association appears to increase with repeated exposure to gadolinium. Since nephrogenic systemic fibrosis may be clinically occult, its prevalence may be higher than reported. Despite this association, it is unclear if gadolinium is the sole or most important factor in the pathogenesis of the disease.

Keywords: chronic kidney disease; end stage renal disease; gadolinium; magnetic resonance imaging; metabotropic glutamate receptors; nephrogenic systemic fibrosis

Introduction

Nephrogenic fibrosing dermopathy, otherwise known as nephrogenic systemic fibrosis (NSF), is an acquired, systemic disorder with prominent skin manifestations occurring exclusively in patients with altered renal function [1]. Clinical manifestations include reddened or darkened patches, papules or plaques. Skin texture may be ‘woody’ and resemble the peel of an orange. Patients may report burning, itching or sharp pains in involved areas [2]. The lesions most commonly involve skin between the ankles and thighs and between wrists and upper arms, and typically spare the face [3]. Although initially considered to affect skin exclusively, NSF was subsequently demonstrated to involve internal organs (skeletal muscle, myocardium, lung, pleura and pericardium) in some patients [4,5].

Skin biopsy reveals proliferation of spindle shaped and elongated fibroblasts and thickened collagen bundles. Recently, Cowper demonstrated that most of these dermal spindle cells contain CD 34 and procollagen I [5]. Interestingly, these markers are present on ‘circulating fibrocytes’, bone marrow-derived cells that migrate to sites of tissue injury.

The aetiology of NSF remains unclear. Most patients are receiving chronic renal replacement treatment when they develop NSF, and 10% have never been dialysed [6]. The cause of renal disease does not seem to bear any relationship to the occurrence of NSF. Anti-phospholipid antibodies may be more...
common in dialysis patients with NSF than in dialysis patients with normal skin, but a strong association of an inflammatory or biochemical marker with NSF has not been confirmed [7]. Likewise, other potential aetiologies of NSF (immunosuppressive medications, erythropoietin (EPO) treatment [8] and surgical procedures) are speculative at best [2]. Several recent reports incriminate exposure to gadolinium during magnetic resonance imaging (MRI) tests as a specific trigger for the development of NSF [9–11].

In this report, we analyse the prevalence of NSF and estimate its association with exposure to gadolinium in a large population of patients with chronic kidney disease (CKD), both dialysis-dependent and predialysis. We also present the possibility that patients may manifest NSF subclinically.

Methods

Identification of NSF in patients on chronic renal replacement

The faculty members of the Nephrology Division at the Medical University of South Carolina (MUSC) care for chronic ambulatory dialysis patients in clinics of two types: (i) 7 neighbourhood-based units in cooperation with Dialysis Clinic Incorporated (DCI, Nashville, TN, USA) and (ii) the affiliated Veterans Administration hospital, 95% in the former and 5% in the latter. From 2001 through 2006, 849 peritoneal dialysis and haemodialysis (HD) patients in the DCI units were under our care. Cases with NSF were ascertained by discussion with all faculty members of the Nephrology Division, by discussion with faculty members of the Department of Dermatology, and by review of all dermatopathology records. The 849 patients were stratified by number of episodes of gadolinium exposure: 0, 1 and greater than 1. We used the Pearson exact Chi-squared test and the Cochran-Armitage test to search for a statistical association between gadolinium exposure and NSF rate and to determine whether the rate of NSF occurrence is a function of increasing number of gadolinium exposures, respectively.

Identification of NSF in patients with chronic kidney disease not on dialysis

From 2004 through 2006, 6636 adult individuals received intravenous gadolinium for MRI enhancement in the Radiology Department at MUSC Hospital. During the same period of time, at the private hospital in the area additional 8169 gadolinium enhanced procedures were performed in patients older than 20 years. Based on National Health and Nutrition Examination Survey (NHANES) data [11], we estimated that 592 of them (4%) had Stage 3 or Stage 4 CKD (estimated glomerular filtration rate 15–60 ml/min). Inquiry for cases of NSF among these patients was made at all dermatology and dermatopathology practices in Charleston County as well as at the Department of Dermatology at MUSC.

Results

Association of exposure to gadolinium with development of NSF in patients on chronic renal replacement therapy

We explored the association of gadolinium with NSF in 849 chronic dialysis patients at MUSC hospital. Chart reviews revealed that among these 849 patients, 261 had undergone 354 MRI scans with intravenous gadolinium enhancement. In all 354 studies, the particular gadolinium preparation was gadodiamide (Omniscan). Gadodiamide was administered to 191 patients once, 52 patients twice, 13 patients thrice and 5 patients four times. Four cases of NSF were identified clinically and confirmed by skin biopsy. Thus, the overall rate of NSF was 0.5% (4 of 849 patients).

When all 849 patients were stratified into categories of the number of gadodiamide exposure (never, once and more than once), rates of NSF were found to be 0% (0 of 588 patients), 1.1% (2 of 191 patients) and 2.9% (2 of 70 patients), respectively. The Pearson exact Chi-squared test demonstrated a strong statistical association between gadodiamide exposure and NSF rate, \( P < 0.01 \). The Cochran-Armitage test for trend yielded a highly statistically significant slope [1.9, 95% confidence interval (CI) 0.4–4.0] of the relationship between the number of gadodiamide exposures and NSF. From this trend analysis, we generated estimated odds ratios for each category of gadodiamide exposures and NSF. From this trend analysis, we generated estimated odds ratios for each category of gadodiamide exposures and NSF. From this trend analysis, we generated estimated odds ratios for each category of gadodiamide exposures and NSF. From this trend analysis, we generated estimated odds ratios for each category of gadodiamide exposures and NSF. From this trend analysis, we generated estimated odds ratios for each category of gadodiamide exposures and NSF. From this trend analysis, we generated estimated odds ratios for each category of gadodiamide exposures and NSF.

Skin biopsy processing and immunostaining for histological diagnosis of NSF

Skin biopsy specimens were fixed in formalin and stained with haematoxylin and eosin. Immunoperoxidase staining for CD34 expression was performed on the same formalin-fixed paraffin embedded tissue. Four micron sections were prepared and mounted on coated slides. The slides were placed in an oven heated to 60°C for 60 min, deparaffinized in xylene and rehydrated through graded alcohols. Antigen retrieval was accomplished via incubation with DAKO Target Retrieval solution (citrate buffer pH 6.1) diluted 1:10 and pre-heated in a steamer to 95°C for 20 min. After rinsing with Tris buffered saline with Tween, sections were incubated with CD34 primary antibody (DAKO, clone QBEnd 10, ready to use) for 30 min and then incubated with DAKO Envision detection reagents and developed with diaminobenzidine (DAB, DAKO). Sections were counterstained with haematoxylin and coverslipped with a permanent mounting medium.
replacement therapy, is not a strong individual predictor of developing NSF.

Three of the four patients received gadolinium once before developing NSF, while one patient was exposed four times. In all cases the dose of gadolinium was 7.5–10 mmol, and skin lesions appeared within 2–3 months of exposure. In one patient, skin lesions improved after living related kidney transplant (Figure 1, colour images are available as Supplementary material), and in two others the lesions remained stable during chronic dialysis. The natural history of NSF in the fourth patient merits additional comment (Figure 2). A 34-year-old Caucasian female with nephritis from systemic lupus erythematosus (SLE) was started on chronic HD and underwent MRI of the brain with gadodiamide (7.5 mmol) for evaluation of headache and visual changes. Within 2 months of exposure, she noted skin changes involving both distal lower extremities (Figure 3, colour images are available as Supplementary material). Skin biopsy showed an increase in CD34-positive spindle and stellate fibroblasts among thickened collagen bundles throughout the dermis and septae of the subcutaneous fat. Mucin was readily detectable among the dermal collagen bundles (Figure 4A and C, colour images are available as Supplementary material). A diagnosis of NSF was made by the dermatology service. After 8 months of HD treatment, she recovered enough renal function (serum creatinine concentration 3.6–4.1 mg/dl) that chronic dialysis could be discontinued. After 6 weeks without dialysis her skin lesions began to abate and after 8 weeks without dialysis skin appeared completely normal. Six months after clinical remission of NSF, the patient underwent a second brain MRI with gadodiamide (7.5 mmol) exposure, but skin lesions did not recur. She remained free of the need for HD for more than 30 months with serum creatinine concentrations ranging between 2.3 and 2.8 mg/dl. A follow-up biopsy (Figure 4B and D) of clinically normal skin adjacent to the site of her first biopsy was performed 18 months after the second gadodiamide exposure. On routine examination, dermal cellularity was normal and cellularity of the septae in the subcutaneous fat was slightly increased. Collagen bundles were slightly thicker and more hyalinized than normal (Figure 4B). CD 34-positive dermal dendrocytes were observed throughout the dermis, consistent with NSF (Figure 4D).
Biopsy-documented NSF was observed in a fifth HD patient from our Veterans Administration hospital affiliate after two exposures (20 mmol each) to gadopentetate (Magnevist) and one exposure (20 mmol) to gadobenate (Multihance). We excluded this patient and the rest of the Veterans Administration patients from statistical analysis because the chronic dialysis population at the Veterans Administration hospital is small and because the patient did not receive gadodiamide like the MUSC hospital patients.

All five of the patients who developed NSF had been exposed previously to immunosuppressive medications, three for kidney transplantation and two for SLE. At the time of gadolinium exposure one patient with SLE received 750 mg of intravenous cyclophosphamide and the second patient with SLE had been on mycophenolate mofetil for several months. Of the transplant patients, one had been on cyclosporine and prednisone over the previous 9 years for combined heart and kidney transplant and was receiving peritoneal dialysis for 5 months due to kidney graft failure at the time of gadolinium exposure. Each of the remaining two patients had two failed kidney allografts and received treatment with cyclosporine, tacrolimus and mycophenolate mofetil for a total of 9 and 11 years, respectively. One patient was still on prednisone at the time of gadolinium exposure, and immunosuppression was stopped 5 months prior to the gadolinium study in the second patient.

Biochemical variables, dialysis modality and EPO-$\alpha$ requirement at the time of gadolinium exposure for all five patients are presented in Table 1. Only three patients were receiving treatment with EPO, all had low serum albumin and only one had significantly
None of the patients who were maintained on HD received additional treatment after gadolinium study.

Association of exposure to gadolinium with development of NSF in patients with chronic kidney disease not on dialysis

We failed to identify NSF in patients with CKD exposed to gadodiamide at MUSC and private Hospital from 2004 through 2006. Of the 14805 patients exposed to gadodiamide over this time period, we estimated that 592 had Stage 3 or Stage 4 CKD. Therefore, the rate of development of NSF in patients with stage 3 and 4 CKD after gadodiamide exposure is very low, certainly <0.2%.

Table 1. Biochemical variables, dialysis modality and erythropoietin (EPO) requirement in patients with NSF at the time of gadolinium exposure

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis modality</td>
<td>CAPD</td>
<td>CCPD</td>
<td>HD</td>
<td>HD</td>
<td>HD</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/l)</td>
<td>3.35</td>
<td>1.38</td>
<td>1.58</td>
<td>1.74</td>
<td>1.55</td>
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<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.02</td>
<td>2.1</td>
<td>2.1</td>
<td>2.0</td>
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<tr>
<td>Serum albumin (g/l)</td>
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<td>32</td>
<td>27</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Dose of EPO (μ/kg)</td>
<td>20</td>
<td>Not on EPO</td>
<td>180</td>
<td>Not on EPO</td>
<td>20</td>
</tr>
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CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous cycler-assisted peritoneal dialysis; HD, haemodialysis.

NSF is a debilitating disease of unknown aetiology. Renal failure appears to be an invariable pre-condition, especially end stage renal disease (ESRD) with chronic renal replacement therapy. All five of our patients with NSF had been exposed to immunosuppressive medications, either in support of a renal allograft or for treatment of renal manifestations of SLE, however, there are no convincing evidence that they play role in the development of the disease.

Recently, it was proposed that contrast media containing gadolinium might be a trigger for NSF [9–11]. From a chronic dialysis population of over 800 patients, we report five patients who underwent an MRI with exposure to a gadolinium-containing compound and developed NSF at a later time. We document an association between exposure to gadodiamide and development of the disease in dialysis-dependent patients. Furthermore, this association increased with more exposures to the agent. In CKD patients not yet on dialysis, no cases of NSF were observed. Despite the association documented between

Fig. 4. Histologic changes of two skin biopsies of patient outlined in Figure 2. Panels A and C represent first biopsy. (A) There is increased cellularity throughout the dermis. The collagen bundles are mildly thickened (original magnification 100×). (C) There are increased CD34 positive fibrocytes throughout the dermis (original magnification 100×). (B and D) represent follow up skin biopsy 2 years later. Panel B: dermal cellularity is markedly reduced compared with the biopsy from 2 years before (original magnification 100×). D: CD34 positive spindle cells remain increased throughout the dermis consistent with residual disease (original magnification 100×).
NSF and gadolinium in ESRD patients, a causal relationship between gadolinium and the development of NSF cannot be confirmed at the present time. The incidence of the disease is very low, and the vast majority of dialysis patients who receive intravenous gadolinium do not develop NSF. The natural history of NSF in one of our patients further illustrates the vague nature of the association between gadolinium and NSF. After this dialysis patient developed NSF after exposure to gadolinium, skin lesions disappeared when her renal failure partially resolved. However, a second exposure to gadolinium did not provoke a relapse of NSF and her skin remained clinically normal. This patient also raises the possibility that NSF may occur subclinically and thus more frequently than proposed, since biopsy of normal-appearing skin showed the pathological hallmarks of the disease.

The mechanism by which exposure to gadolinium might participate in the development of NSF is not clear. Although gadodiamide has been involved in the majority of NSF cases, gadolinium coupled to other anions has been associated with the disease, as occurred in our fifth case and has been reported by others [12]. Therefore, NSF appears to be associated with the gadolinium ion rather than a specific gadolinium-containing agent. The hypothesis that accumulation of gadolinium in the skin plays a pathogenic role in the development of NSF remains tenuous until its absence in the skin of patients with ESRD exposed to this agent without the disease is thoroughly demonstrated. It has been suggested that higher serum concentrations of ionized calcium and phosphate as well as high dose EPO-β treatment increase the risk of gadolinium related NSF [13]. In our series, two patients were on rather modest dose of EPO-α (EPO-α is used in North American patients), and two had not received it at all at the time of exposure to gadolinium. Likewise, levels of calcium and phosphorus except in one patient were not elevated.

Gadolinium has long been known to bind to class C-type G-protein coupled receptors including the calcium sensing receptor and metabotropic glutamate receptors [14,15]. It has been recently reported that binding of gadolinium to the metabotropic glutamate 1z-receptor results in a shift toward Gq-mediated intracellular signalling when activated by glutamate, which is different from the typical mixed Gs/Gq-mediated signalling [16]. Gadolinium can also alter the intracellular calcium response to exogenous homocysteine through the calcium sensing receptor (M. Janech, personal communication). Therefore, extracellular gadolinium may modify intracellular signalling through G-protein coupled receptors known to play a role in skin differentiation. Because homocysteine activates certain metabotropic glutamate receptors [17], it would be interesting to evaluate the role of homocysteine in patients exposed to gadolinium who developed NSF. Hyperhomocysteinaemia has been implicated in the pathogenesis of a number of skin diseases including chronic cutaneous wounds, SLE, psoriasis, Behcet’s disease [18] and a child with homocystinaemia developed NSF after gadolinium exposure [19].

Reports of the suggested linkage between gadolinium and the development of NSF have dampening the enthusiasm of radiologists for administering gadolinium to patients with any level of renal impairment [12]. Thus, it has become difficult for clinicians to obtain high resolution imaging with enhancing agents for patients with renal insufficiency. Computerized tomography with iodinated dye enhancement is a risk factor for worsening of pre-existing azotaemia, and MRI with gadolinium enhancement may be a risk factor for the development of NSF. Based on our experience, it is premature, certainly, to restrict exposure to gadolinium in patients with Stages 3 or 4 CKD. One potential strategy would be to opt for computerized tomography with iodinated dye in patients already begun on chronic renal replacement therapy and reserve MRI with gadolinium for patients with CKD not yet on dialysis. Efficacy of this strategy would be limited by allergies to iodinated dyes and the high risk of loss of residual renal function after iodinated dye exposure in peritoneal dialysis patients, who are often dependent on residual renal function.

Since about 30% of our chronic dialysis patients were imaged with gadolinium enhancement, it appears that important clinical information has been and will continue to be garnered from MRI studies utilizing gadolinium. If gadolinium MRI is required in dialysis patients, careful monitoring of their skin for development of NSF should be performed for at least 4–6 months after exposure, keeping in mind that early lesion may be subtle. Although efficacy is not proven at this point, performing HD immediately after gadolinium exposure may be reasonable [12]. Beneficial effects of photopheresis on NSF have been recently reported [20]. Until these encouraging results are confirmed, improvement in renal function, predominantly by kidney transplantation, remains the only effective means by which NSF can be ameliorated. Giving priority on the transplant waiting list to the patients with this debilitating condition should be encouraged, as recently suggested by Cowper [6].

Supplementary Data

Supplementary Data are available at NDT Online.

Conflict of interest statement. None declared.


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