New Insights into Nephrogenic Systemic Fibrosis

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ABSTRACT

Nephrogenic systemic fibrosis is a new disorder reported almost exclusively in patients who have renal insufficiency and are exposed to contrast media formulated with gadolinium. High morbidity and mortality are associated with this severely disabling and painful condition. The acute phase begins upon exposure to gadolinium contrast media, characterized by a systemic inflammatory response involving iron mobilization, and then as a progressive, chronic phase in which fibrosis develops. Proposed is a unifying model of cumulative risk factors in which the interplay of systemic inflammation and stimulated hematopoietic environment associated with hyperparathyroidism and erythropoietin may tie to a common pathogenic mechanism of fibrogenesis. Because there are no uniformly effective interventions to treat nephrogenic systemic fibrosis other than successful renal transplantation, prevention by avoiding gadolinium contrast media in patients with chronic kidney disease is vital. On the basis of suspected pathogenesis, it is also reasonable to limit erythropoietin and iron therapy to dosages ensuring recommended targets and adequately control hyperparathyroidism. Herein is reviewed what is currently known about this subject.


Nephrogenic systemic fibrosis (NSF) is a recently described systemic fibrosing disorder that has been reported almost exclusively in patients with renal insufficiency. It was first described by Cowper et al. in 2000 as a cutaneous scleromyxedema-like disorder in patients with ESRD and was initially called nephrogenic fibrosing dermopathy. Clinical and autopsy data now suggest the presence of a systemic fibrogenic reaction with evidence of involvement of muscle, tendons, diaphragm, testes, cardiac atrium, lungs, and duramater. The disease henceforth has been referred to as nephrogenic systemic fibrosis.

More than 200 cases of NSF have been reported to the Food and Drug Administration and to the NSF registry at Yale University. The estimated prevalence of NSF, however, is likely to be inaccurate because it still is not a widely recognized clinical entity. In addition, subclinical forms of NSF that could be recognized only with a skin biopsy might remain undiagnosed. In this review, we describe novel clinical manifestations of NSF and discuss our views on its pathogenesis. Specifically, we present a general paradigm in which different risk factors may be tied to a common pathogenic mechanism.

CLINICAL AND LABORATORY FEATURES

NSF is a severely disabling systemic fibrosing condition associated with increased morbidity and mortality. Our observations suggest that clinical features of NSF may include an acute phase that immediately follows exposure to gadolinium-based contrast media (GBCM) and an overlapping chronic phase characterized by progressive fibrosis (Table 1). Features in the acute phase are variably present and mimic systemic inflammatory response

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syndrome: Fever, hypotension, acute kidney injury, anemia, leukoerythroblastic picture, thrombocytopenia or thrombocytosis, leukocytosis, eosinophilia, monocytosis, elevated γ-glutamyl peptidase, elevated lipase, and elevated D-dimer. Decreased total iron-binding capacity, elevated serum ferritin, low serum albumin, and elevated C-reactive protein are invariably present. Because many patients have critical illnesses such as sepsis, acute pancreatitis, hepatorenal syndrome, or acute graft dysfunction that precedes NSF, the acute phase of systemic fibrogenesis may go unrecognized. Onset of the chronic phase is also variable: As early as 4 or as late as several months after GBCM exposure. Early cutaneous manifestations in the chronic phase are usually limited to generalized edema followed closely by the development of a plaque-like skin rash with woody induration (Figure 1A). The condition tends to affect either dependent parts of the body, such as extremities or the presacral area, or high blood-flow areas, such as the skin overlying an arteriovenous dialysis fistula. Facial tremities or the presacral area, or high blood-flow areas, such as sepsis, acute pancreatitis, hepatorenal syndrome, or graft-versus-host disease. An absence of facial involvement and circulating paraprotein, temporal relation to GBCM exposure, and the appropriate clinical context helps in differentiating NSF from these other conditions.

**RISK FACTORS FOR NSF**

The major risk factors associated with NSF include exposure to GBCM,9,16,17 high-dosage erythropoietin (EPO) therapy,7 elevated parathyroid hormone (PTH),7 hypothyroidism,17 and antiphospholipid antibodies.17 Significant vascular disease is also a risk factor.17 On the basis of current understanding, an interaction of low GFR; exposure to GBCM; and presence of additional risk factors such as high-dosage EPO, elevated PTH, vascular disease, and systemic inflammation seem necessary for the development of NSF in the majority of cases. In this “cumulative risk factor model” proposed by us and detailed in the following section, patients with more cumulative risk (risk factor load) may only need low dosages of GBCM to trigger NSF or vice versa (Figure 2).

**IMPAIRED RENAL FUNCTION**

NSF is seen in patients both with acute kidney injury and with chronic kidney disease (CKD). No specific cause of kidney disease except hepatorenal syndrome15 has been associated with heightened risk. NSF is seen in patients receiving either hemodialysis or peritoneal dialysis as well as in patients with posttransplantation allograft dysfunction. Singularly, a low GFR is a major prerequisite for NSF to develop. In patients with CKD, on the basis of current reports as well as personal observations, the risk for NSF seems to be limited to those with stage 3 or worse CKD (GFR ≤60 ml/min). Recently, Sadowski et al. reported the risk for NSF after gadolinium exposure at various levels of estimated GFR (eGFR), and in their series, NSF developed predominantly in those with eGFR <30 ml/min.10 NSF also developed in two patients with an apparently higher eGFR in the setting of acute kidney injury, where formula-based estimates for GFR cannot be used. In our personal experience, we have observed, after GBCM exposure, that NSF can develop in patients with an eGFR as high as 40 ml/min. However, imprecision of formula-based eGFR in accurately predicting renal function in stage 3 CKD limits our ability to interpret these findings18 or arrive at a precise and safe cutoff of GFR above which the risk for NSF is negligible.
GADOLINIUM TOXICITY: ROLE OF IRON AND TRANSMETALLATION

In addition to several reports on the epidemiologic association of GBCM exposure and NSF, demonstration of gadolinium in NSF tissues has strengthened the causal link between the two. A higher dosage and multiple repeated exposures to GBCM increase the risk for NSF. The mechanisms through which administration of GBCM results in toxicity and NSF are still evolving. However, several important clues appear from current published literature. First, overt NSF develops in only 3 to 5% of patients after GBCM exposure. Second, some patients with NSF do not manifest any clinical signs, even when they were previously exposed to GBCM. Third, demonstration of significant quantities of insoluble gadolinium in the skin of patients with NSF, months after GBCM exposure and after extensive tissue processing, suggest that gadolinium might have undergone transmetallation in vivo. This finding is of significance because free gadolinium is toxic.

Supporting the importance of transmetallation, all NSF cases reported thus far have been associated with linear magnetic resonance contrast agents that have inferior thermodynamic stability and a kinetic or conditional stability that favors transmetallation. The mechanism by which GBCM
may undergo transmetallation \textit{in vivo} or cause toxicity is still under investigation. In an initial report, acidosis was thought to induce gadolinium’s dissociation from its chelate\textsuperscript{16}; however, a subsequent report failed to confirm this.\textsuperscript{9} Administration of magnetic resonance contrast agents is widely known to cause transient (up to 72 h) elevations in serum iron, even in 15 to 30% of healthy volunteers.\textsuperscript{27,28} Because iron is tightly bound to ferritin and hemosiderin, it has been suggested that its free concentration is insufficient to induce transmetallation of GBCM\textsuperscript{25,29}; however, we recently reported that GBCM administration in patients who have CKD and subsequently develop NSF results in a marked decrease in total iron-binding capacity, iron mobilization, profound transferrin oversaturation, and systemic inflammation.\textsuperscript{8} In patients with renal insufficiency, several factors may aggravate free iron release, including prolonged retention of GBCM (t\textsubscript{1/2} 13.4 to 89.2 h versus 1.5 h controls),\textsuperscript{30} additional exogenous treatment with parenteral iron and low total iron-binding capacity secondary to malnutrition, urinary protein (transferrin) loss, sepsis, and chronic inflammation.\textsuperscript{31–33} Available data suggest that iron is most potent in inducing transmetallation of GBCM because the thermodynamic stability of Fe\textsuperscript{3+}-DTPA-BMA (10\textsuperscript{21.9}) far exceeds the thermodynamic stability constant of gadolinium-DTPA-BMA (10\textsuperscript{16.9})\textsuperscript{34} (Table 2).

Gadolinium-mobilized iron can also be directly toxic to tissues through the induction of oxidative stress by Fenton reaction (Figure 3).\textsuperscript{35} In addition, catalytic iron released by systemic inflammation\textsuperscript{35} and gadolinium-mediated cellular acquisition of catalytic gadolinium chelates by endogenous ions: The role of iron.

### Table 2. Potency of various endogenous cations in inducing transmetallation of gadolinium-DTPA-BMA\textsuperscript{a}

<table>
<thead>
<tr>
<th>Cation-DTPA-BMA</th>
<th>(\log K_{\text{therm}})</th>
<th>Transmetallation Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>10\textsuperscript{7.2}</td>
<td>+</td>
</tr>
<tr>
<td>Zinc</td>
<td>10\textsuperscript{12}</td>
<td>++</td>
</tr>
<tr>
<td>Copper</td>
<td>10\textsuperscript{13}</td>
<td>++</td>
</tr>
<tr>
<td>Gadolinium</td>
<td>10\textsuperscript{16.9}</td>
<td>–</td>
</tr>
<tr>
<td>Iron</td>
<td>10\textsuperscript{21.9}</td>
<td>++++</td>
</tr>
</tbody>
</table>

\(K_{\text{therm}}\) is a thermodynamic stability constant. The plus and minus symbols refer to the degree of potency. +, mild; ++, moderate; ++++, strong; −, n/a.

### ROLE OF EPO, INFLAMMATION, AND VASCULAR INJURY

We and others\textsuperscript{7,17,40} recently reported that patients with NSF also receive higher dosages of EPO, suggesting that EPO might play a role in pathogenesis. On the basis of our clinical experience with 70 patients with NSF and other available large case series,\textsuperscript{7,8,17} it is uncommon that patients do not receive any EPO before NSF diagnosis. It is possible that endogenous EPO released during stress-induced erythropoiesis, which could be several hundred-fold,\textsuperscript{41} or other growth factors that synergize with EPO\textsuperscript{42} might be important in patients who do not receive exogenous EPO before a diagnosis of NSF. In addition, in applying the cumulative risk model (Figure 1), exogenous EPO may not be a necessary prerequisite in all cases.

There are many compelling reasons for why EPO might participate in the pathogenesis of NSF. Its pleiotropic biologic effects and/or systemic inflammation associated with an EPO-resistant state may be important (Table 3). Theoretically, EPO therapy influences all key elements of the pathogenesis of NSF: Endothelial dysfunction, inflammation, cell proliferation, and

### Table 3. Potential role of EPO in the pathogenesis of NSF

- Endothelial dysfunction increases
  - endostatin
  - asymmetric dimethyl arginine
- Proinflammatory increases
  - monocyte chemoattractant protein-1
- Cell proliferation increases
  - endothelial cells
  - smooth muscle cells
  - endothelial progenitor cells
wound healing. EPO is a potent cytokine with stimulatory effects on vascular endothelium, smooth muscle cells, and platelets. EPO administration induces a release of vasoactive factors such as monocytic chemoattractant protein-1, endothelin-1, thromboxane A2, and selectin. It can also induce endothelial dysfunction by inhibiting dimethylarginine dimethylaminohydrolase, thereby increasing asymmetric dimethyl arginine. Furthermore, EPO is a potent stimulant of endothelial and progenitor cell proliferation, as well as wound-healing responses that are reminiscent of histologic changes seen in NSF. EPO and PTH are also strong stimuli for a systemic release of CD34 progenitor cells, which are known to participate in wound healing. Vascular endothelial cell injury could similarly contribute to the pathogenesis of NSF by inducing the release of vasoactive factors and CD34 progenitors, and in this setting, EPO's detrimental effect on endothelia is further aggravated. In addition, chronic inflammation associated with an EPO-resistant state effects on vascular endothelium, smooth muscle cells, and high-dosage EPO might also contribute to the fibrogenesis seen in NSF.

CELLULAR BASIS FOR THE PERSISTENCE OF FIBROSIS IN NSF

As with any other systemic fibrosing condition, possible origins of fibroblasts in NSF include resident mesenchymal cell populations, epithelial-to-mesenchymal transition of local epithelia, and bone marrow–derived cells. Cowper and Bucala demonstrated that the spindle cells in NSF skin lesions express CD34 and procollagen 1 and suggested that circulating fibrocytes mediate the fibrosis in NSF. Even though the presence of these markers suggests a contribution from circulating fibrocytes, it is important to note that these markers are not unique to fibrocytes; fibrocyte's contribution to fibrosis is highly variable in different organs and is affected by additional factors such as cell turnover rates. Supporting this, Fathke et al., using cross-transplantation (bone marrow) experiments in an EGFP transgenic mouse model, nicely demonstrated that both CD45+ and CD45− bone marrow–derived stem cells contribute to dermal collagen deposition and wound repair. In addition, they observed a role for local dermal cells and endothelial progenitor cells in dermal wound healing. Similarly, using tissue reconstitution experiments with single hematopoietic stem cells (HSC), Ogawa et al. showed that HSC significantly contribute to myofibroblast population in tissues. EPO, PTH, and an oxidative stress-induced "stimulated hematopoietic environment" may thus contribute to fibrosis through increased production of tissue myofibroblasts. It is unknown, however, whether fibrocytes are a necessary intermediate in this process of transformation of HSC into myofibroblasts in vivo; therefore, it is likely that both resident fibroblasts and diverse types of bone marrow–derived cells that are released in response to injury and cytokines such as EPO, including HSC (likely to be the most significant contributor), endothelial progenitor cells, mesenchymal precursors, and monocyte-derived cell fibrocytes, contribute to fibrosis in NSF (Figure 4). Any contribution of epithelial-to-mesenchymal transition to fibrogenesis in NSF, although potentially possible, has not been evaluated. Like other chronic fibrosing disorders, persistent or progressive fibrosis, even after the original trigger is removed, may lead to NSF. This occurrence possibly relates to the concept of a "persistently activated fibroblast phenotype," which could be mediated by factors such as ongoing chronic endothelial injury in uremia.

TREATMENT

There are no good therapies for the cutaneous symptoms of NSF or, more important, to prevent its associated high mortality; therefore, our first recommendation is prevention. On the basis of the available data and our personal experience, we recommend the following measures for NSF prevention:

Renal function should be checked in all high-risk patients before GBCM administration (age >50 yr; infants; history of renal disease, diabetes, hypertension, or liver disease; and critically ill patients). Avoid GBCM in patients with an eGFR <40 ml/min. If clinically indicated and benefits outweigh risks, then use low dosages of GBCM (preferably macrocyclic agents) in patients with an eGFR of 40 to 60 ml/min. GBCM is absolutely contraindicated in patients who are on peritoneal dialysis, because gadolinium is poorly cleared by the peritoneum.

In patients who are on hemodialysis, GBCM should be administered only if the benefits of obtaining a contrast-enhanced magnetic resonance image substantially outweigh the risk. At the completion of imaging, patients should go directly to the dialysis machines, if possible. Any patient who is less than 18 yr old, with an eGFR >60 ml/min, who has either diabetes or chronic kidney disease, or who is on immunosuppressive therapy, should avoid GBCM. If GBCM is needed in these patients, administer a dose of 0.01 mg/kg of EDRF or 0.02 mg/kg of BEIRF, or the equivalent macrocyclic agent, at the time of the GBCM administration.

Figure 4. Cellular basis for fibrosis in NSF: Interaction of multiple risk factors and central role of hematopoietic stem cells.
to the hemodialysis unit for initiation of dialysis, and dialysis treatment should be administered for 3 consecutive days.

Avoid intravenous iron immediately before or after GBCM exposure.

Treatment of NSF involves a multidisciplinary approach. Aggressive physical therapy, pain control, and psychologic support are essential cornerstones of therapy in this severely disabling disease. The severity of pain usually necessitates opiate analgesics. Topical treatments include the use of moisturizers, emollients, and anti-inflammatory creams. Deep tissue massage and hydrotherapy may be helpful. On the basis of potential pathogenic mechanisms, control of PTH levels and limiting administration of EPO and intravenous iron enough to maintain recommended hemoglobin targets are likely to help. Limiting systemic inflammation by decreasing infection episodes such as catheter-related bacteremia may also be beneficial. Other treatment approaches that could result in variable and modest improvements include a combination of hydroxychloroquine and low-dosage steroids (S. Swaminathan, 2006, personal observation), extracorporeal photopheresis, and topical ultraviolet-A therapy. However, none of these options has been uniformly effective in patients with NSF. Renal transplantation that results in a well-functioning allograft usually leads to a substantial resolution of the disease, and maintaining lower cyclosporine and tacrolimus targets may also potentially help in limiting fibrogenesis.72–74 Secondary worsening of NSF after initial improvement but without new GBCM exposure can occur, but the mechanisms involved in these relapses are unclear. No data are available on the benefit of using chelation therapy to remove gadolinium in NSF. A better understanding of the pathogenesis in this devastating disease may lead to new interventions, which may be relevant not only to NSF but other fibrosing conditions.

ACKNOWLEDGMENT

We thank Cindy Reid for technical editing and graphics assistance.

DISCLOSURES

None.

REFERENCES


