Review

Nephrogenic systemic fibrosis. A debilitating disease causing fibrosis of the skin and inner organs in patients with kidney failure

H. Pieringer and G. Biesenbach

Section of Rheumatology and Section of Nephrology, 2nd Department of Medicine, General Hospital Linz, Linz, Austria

Herwig Pieringer, MD
Georg Biesenbach, MD, Professor

Please address correspondence to:
Dr. Herwig Pieringer,
Section of Rheumatology and Nephrology,
2nd Department of Medicine,
General Hospital Linz,
Krankenhausstrasse 9,
A-4020 Linz, Austria.
E-mail: herwigpi@yahoo.com

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ABSTRACT

Nephrogenic systemic fibrosis (NSF) is a rare and debilitating disease which affects patients with kidney failure. The most obvious manifestation is fibrosis of the skin, but it also frequently involves the locomotor system and the inner organs. An association has been found with the administration of gadolinium-containing contrast agents, which are given to provide enhanced contrast during magnetic resonance imaging. It is thought that unstable chelate complexes release toxic gadolinium. Other triggers or co-triggers may also be relevant. No effective treatment currently exists for NSF, so prevention of the disease is of the utmost importance. If gadolinium-containing contrast agents need to be administered to patients who have kidney failure, a cyclic agent should be used, and the dosage should be as low as possible. Although no proof is yet available that hemodialysis prevents NSF, it is effective in the clearance of gadolinium and should therefore be considered as a treatment immediately after the imaging.

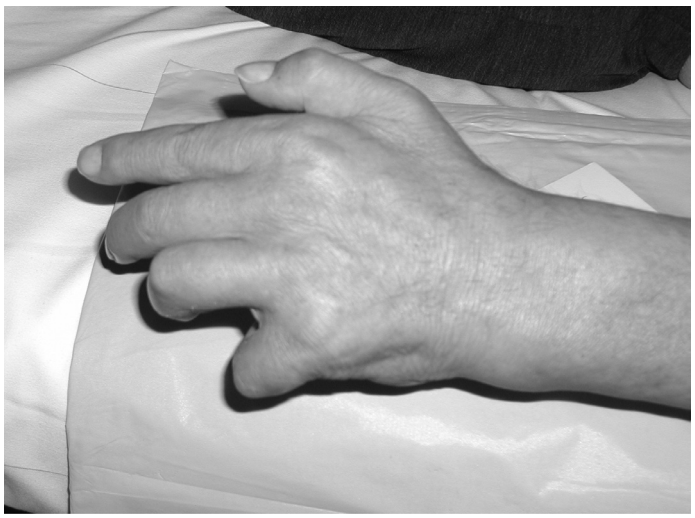
Introduction

Nephrogenic systemic fibrosis (NSF) is a rare and debilitating disorder, which has become evident in clinical practice and research within the last decade. It affects patients with impaired kidney function, many of whom are undergoing haemodialysis. However, it also affects patients who are undergoing peritoneal dialysis, patients who have had a kidney transplant, and patients with advanced kidney failure who are not yet dependent on renal replacement therapy. One of the most evident clinical signs of the disease is marked fibrosis of the skin (1), which gave rise to the original name for the disease: nephrogenic fibrosing dermopathy. When it became clear that other tissues, such as the locomotor system and even inner organs, are frequently involved, the name of the disease was changed to the broader term: NSF.

The first NSF cases were recognised after 1997, when similarities to scleromyxedema were described (2). It is believed that the disease did not exist before 1997. This assumption is based on the fact that preserved tissue samples taken before that time did not show any characteristic signs of NSF (1). This finding has raised the suspicion that external factors may cause the disease.

Clinical picture

The most evident sign of NSF is fibrosis of the skin, usually more severe in the more distal areas of the extremities (3). There are similarities to scleroderma (4). However, NSF usually does not affect the head (3, 5). Even in the early stages of NSF, when oedema may be present (5), the clinical picture can resemble scleroderma. As the disease progresses, the fibrosis of the skin becomes the dominant symptom. There may be fibrotic papules, plaques, and nodules in the subcutaneous tissue as well as alterations in pigmentation (3). These changes can also affect deeper tissues, *e.g.* the locomotor system (6, 7). resulting in contractures of the joints (3, 5, Fig. 1a). In such severe cases, the function of the fingers and hands is impaired. Contractions may also affect the hips, elbows, and knees so that the patient's mobility can be limited, and walking aids may be necessary (6). Movement required for daily living can become impossible, and patients are sometimes dependent on other people for assistance. Figures 1a and 1b show the characteristic signs of skin changes



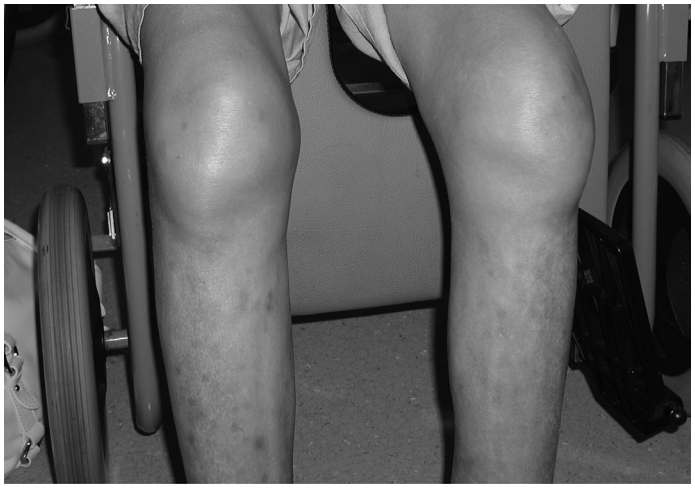


Fig. 1a, 1b. Contractions of the joints may limit the mobility and function of the hands.
Fibrosis and pigmentation of the skin on the shins in a patient with NSF.

and contractions in patients affected by NSF. Although the skin is the tissue most frequently involved, inner organs such as the lungs, the myocardium, the diaphragm, and even the dura mater can also be affected (3, 6, 8, 9). The length of time until a patient with end stage kidney failure develops NSF varies greatly: reports range from as short as a few months to as long as 15 years (3). Whether the disease affects survival is not clear. Some authors have reported cases in which mortality was linked directly to NSF (10), while others did not uncover increased mortality (11).

Histopathology

Biopsies of the skin and organs involved show characteristic histological changes. Light microscopy shows fibrotic lesions with the deposition of abounded collagen bundles and significant accumulation of mucin (6). A large number of spindle-shaped and elongated cells are present (1, 6). The changes in the dermis usually extend to the subcutaneous tissue, where septa are widened due to collagen deposits (3, 6). In severe cases, the number of collagen bundles can be excessive, and the fibrotic process may extend through the fascia and into the underlying skeletal muscle. Immunohistochemical staining demonstrates the presence of CD34+ cells, which are thought to resemble attracted circulating fibrocytes (3, 12). In addition, cells that are positive for CD68 and/or the factor XIIIa, resembling dendritic cells (3, 8), are also present. One theory proposes that these cells may enhance the fibrotic process by the production of TGFβ (6). Special testing has also demonstrated the presence of gadolinium in the affected tissue of some NSF patients (13, 14). Figures 2a and 2b show the histopathologic changes in a patient with NSF.

Pathogenesis

Following the initial recognition of NSF, it was noted that the disease seems to be associated with the use of the gadolinium-containing contrast agents (G-CAs) used for magnetic resonance imaging (MRI) (15). The G-CA most frequently reported in association with NSF is gadodiamide, but NSF cases who received other G-CAs have also been identified (16). Initially, this association was rather speculative, but the evidence has become increasingly clearer to the point where the Food and Drug Administration (FDA) has added a warning label about the use of G-CA in patients with kidney failure (17). A number of other authorities, such as the European Medicines Agency (EMEA), as well as national and international societies have also issued warnings about the administration of G-CA in patients with kidney failure and advising screening for impaired kidney function in patients at risk (18-23). These measures demonstrate that NSF is now a global issue.

The toxicity of gadolinium in the case of kidney failure can be explained by the dramatically prolonged half-life of the substance. While for gadodiamide the half-life in healthy people has been reported to be 1.3 hours (± 0.25), this level increases up to 34.3 hours (± 22.9) in patients with stage V chronic kidney disease (CKD) (24). The risk of developing NSF seems to be dose dependent (11, 25), and the deposition of gadolinium has been found within the affected tissue (13, 14). These findings support the hypothesis of the causative role of G-CA in NSF. The risk of developing NSF after each contrast-enhanced MRI study has been reported to be 2.4 % (10). An interpretation of this statistic must take into account the possibility that the pharmacological differences between different types of G-CA may influence the risk of developing NSF. The risk might therefore differ from agent to agent. In summary, a number of reports point to the significant role that gadolinium may play in the development of NSF.

The research indicates that the chelating complexes that bind gadolinium may be unstable, thereby releasing toxic Gd3+

ions (26). As mentioned, in the presence of kidney failure, the half-life of G-CA is dramatically prolonged, which in turn, increases the probability that significant amounts of toxic gadolinium may be released into the tissue. It is also believed that metabolic acidosis may enhance this process. In one small study, patients with metabolic acidosis developed NSF after the administration of G-CA, while those who were not acidotic did not develop NSF (15).

As previously mentioned, in contrast agents, gadolinium is bound in the chelating complexes. These can be divided into linear forms, such as gadodiamide (Omniscan®), gadopentetate dimeglumine (Magnevist®), gadobenate dimeglumine (Multihance®), gadofosveset trisodium (Vasovist®), gadoxetate disodium (Primovist®), and gadoversetamide (Optimark ® – not approved in Europe) (21), and cyclic forms, such as gadobutrol (Gadovist®), gadoterate meglumine (Dotarem®), and gadoteridol (Prohance®) (21). It is believed that the cyclic forms may bind gadolinium more effectively, thereby reducing the probability of releasing it into the tissue (27). Use of these forms of chelating complexes could therefore reduce a patient's risk of developing NSF (28). Furthermore, adding ligands to the G-CA may be beneficial, as they seem to reduce the amount of gadolinium released into the tissue (29).

A further mechanism that may lead to the increased release of gadolinium from the chelating complex is transmetallation. A number of ions, such as iron, calcium, zinc, or copper, may lead to the displacement of the gadolinium ion from its ligand, which can destabilise the complex, enhance the dissociation of the chelating complex, and finally release gadolinium (26, 30, 31). However, whether this effect is clinically relevant has not been determined.

The time after which symptoms of NSF develop following the administration of G-CA varies widely and ranges from two days to as long as 18 months (32). However, in most cases, a period of a few weeks has been reported.

Previous studies have proposed that TGFβ might have a pathogenetic role in the evolution of NSF (3, 6). It was assumed that a causative agent may act as a noxious stimulus with respect to dendritic cells. In response, these cells might increase their production of TGFβ, which could finally result in an enhancement of the fibrotic process and also activate additional dendritic cells, thereby leading to a vicious cycle of the accumulation of mature dendritic cells in the tissues affected (3). Therefore, blockade of the TGFβ-pathway could be a possible therapeutic target (33). Another hypothesis suggests that a causative agent might lead to a bone marrow response, which could increase the release of CD34 + cells. According to this theory, these cells might then accumulate in the affected tissue, increase collagen production, and finally lead to tissue fibrosis (3). Substances which stimulate the proliferation of cells within the bone marrow could enhance this process (see below).

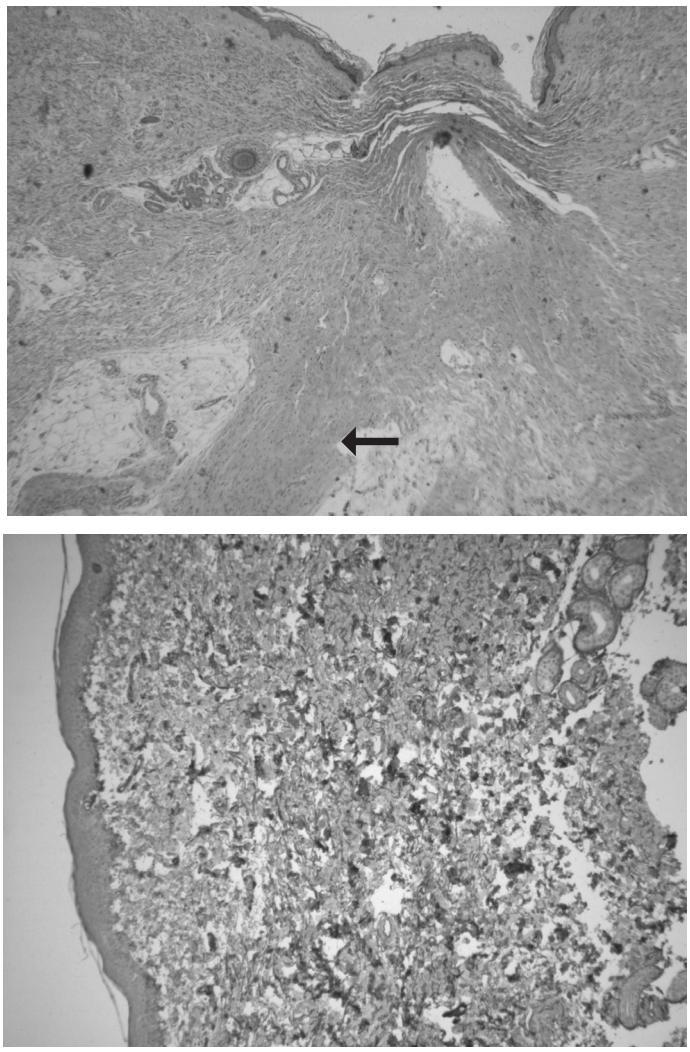


Fig. 2a, 2b. Light microscopy of a skin biopsy of an NSF patient shows fibrotic lesions with deposition of abounded collagen. The arrow marks a septum of collagen bundles that extends from the dermis into the subcutaneous tissue. Immunohistochemical staining demonstrates the presence of CD34+ cells.

It should be noted that some reports of NSF cases show no history of G-CA administration (34-37). In addition, it is not clear why some patients develop NSF after only a single administration of G-CA, while others receive G-CA several times without developing any signs of NSF. This inconsistency has led to the assumption that co-factors might be relevant in the development of NSF. For example, some studies have found higher doses of erythropoietin used in NSF patients than in control groups (38-39). In one of these studies, 50% of NSF patients had been exposed to G-CA (35). It is of interest that the use of erythropoietin in the treatment of renal anemia has been much more common during the past 10 years – a time span that corresponds to the appearance and recognition of NSF. This observation has led to speculation about an interrelation between erythropoietin use and

NSF. One of the fundamental features of NSF is the presence of CD34+ cells within the affected tissue (40). These cells resemble bone marrow stem cells. One hypothesis postulates that erythropoietin might increase the amount of circulating CD34+ precursor cells, which could then migrate to the tissue and enhance the process of NSF. However, it is important to note that in none of the studies mentioned were the authors able to demonstrate a causal relationship between erythropoietin and NSF. It could also be true that higher doses of erythropoietin reflect higher erythropoietin resistance in those patients who develop NSF (26, 35, 38).
Additional triggers or co-triggers that might be relevant in the development of NSF have been reported in the literature: the absence of treatment with ACE-inhibitors (41), prior endothelial damage (33), the presence of infection (42), a pre-existing pro-inflammatory event (43), and chronic inflammation (44). It is important to note that the risk of developing NSF seems to be higher in patients undergoing peritoneal dialysis than in those receiving haemodialysis (36), possibly because the clearance of gadolinium is less effective with peritoneal dialysis than with haemodialysis.

Diagnosis

The clinical picture initially leads the physician to suspect NSF. A biopsy of the skin should be taken in order to prove the diagnosis (31). The effectiveness of the biopsy is enhanced if it contains deeper tissues. In addition to signs of fibrosis, one of the fundamental features of the disease is the presence of CD34+ cells (3).
With regard to laboratory parameters, reduced kidney function needs to be demonstrated; the majority of NSF cases have CKD. About 10% of NSF cases develop in patients with acute kidney injury (16). In some cases, there can be an elevation of the parameters of systemic inflammation, such as C-reactive protein or erythrocyte sedimentation rate (3). To exclude other diseases, one should also include the following tests: anti-nuclear antibodies, thyroid stimulation hormone, serum-electrophoresis, and an eosinophilic count (one would expect these parameters to be within the normal range). It is also important to look for the administration of gadolinium in the patient's history.

Treatment

Currently, there is no effective treatment for NSF. From a theoretical perspective, the restoration of kidney function might be beneficial. Some NSF cases have shown improvement after a kidney transplant (45), the positive effect of which can be attributed to the increased clearance of gadolinium. However, it remains unclear whether this effect is due to the improved kidney function or to other factors, *e.g.* immunosuppressive therapy (23, 45). At this point no proof exists that kidney transplantation is a truly effective form of treatment (46).
Effective intervention has been reported in individual cases. One report indicated that intravenous sodium thiosulfate was beneficial (26). The authors suggested that sodium thiosulfate may chelate gadolinium and enhance its solubility and stability in serum, thereby facilitating its excretion during dialysis. However, the effectiveness of this treatment has been questioned in a further report (47). Another report described a positive effect from intravenous immunoglobulins (48). Two patients had a positive response to imatinib, a small-molecule tyrosine kinase inhibitor that blocks TGFβ signalling, enabling it to reduce the development of fibrosis (33, 49). In these two patients, there was a progressive reduction in skin thickening as well as improvement in joint contractions and the amount of fibrosis found in skin biopsies after the administration of imatinib (400 mg daily). According to the authors, these effects appeared to be reversible after discontinuation of the drug (49). Corticosteroids could theoretically be of benefit because of their broad anti-inflammatory effects and their interference with fibroblast proliferation and collagen synthesis (50), but their administration seems to be without any significant therapeutic effect (51). Some patients seem to benefit from extracorporeal photopheresis, a procedure that leads to increased production of the tumour necrosis factor-alpha, which in turn, could suppress collagen synthesis and enhance collagenase production (52-54). Phototherapy, which inhibits procollagen synthesis, has also been reported to be benefical (55), as has plasmapheresis, which supposedly reduces profibrotic cytokines such as TGFβ (56). In some patients with NSF, fibrosis has been reported to be improved by pentoxyfyllin, which causes some anti-tumour necrosis factor activity. As a non-pharmacological treatment, intensive physiotherapy seems to improve the patient's condition; its application is usually recommended very early in the course of treatment (57).
In conclusion, the literature provides no proof of an efficacious treatment for NSF. The evidence presented in published reports is insufficient to support the effectiveness of any specific treatment. In fact, in our opinion, there is a strong concern about publication bias, as usually only case reports or small case series, which report positive results, are published in the literature. The fact that the benefit of experimental therapies is reported only for single cases should raise suspicion. In the absence of any proven effective treatment for NSF, its prevention is therefore of the utmost importance.

Prevention

Because there is no known effective treatment for NSF, precautions should be taken to prevent its development. G-CAs should not be given to patients with impaired kidney function. This recommendation is generally accepted for patients with a glomerular filtration rate (GFR) of <30 mL/min/1.73m^2. As previously mentioned, the FDA and other authorities have issued a warning for all such patients who are being considered for MRIs (17-23). Even if most NSF cases are related to gadodiamide and if there may be substantial differences between the products available, a possible class effect cannot be excluded, so the warning has been issued for all G-CAs. However, the risk of developing NSF appears to be lower with the use of agents containing cyclic chelating complexes than with linear ones (21). Therefore, the former

are preferred for patients with kidney failure. It must be underlined that currently, no proof has been found that interventions such as haemodialysis can prevent NSF. Therefore, the following recommendations can be seen as general advice to physicians who have patients with impaired kidney function and who undergo MRI tests. It is important to note that these suggested treatment strategies have never been formally tested and that each decision must be based on the individual patient's situation. It should be noted that the estimation of the GFR from the serum creatinine level is reliable only in patients whose kidney function is stable. Therefore, in patients with acute renal failure, when the creatinine level is rising steeply, the actual GFR might be overestimated.

Patients with CKD V

If specific circumstances permit a G-CA application in patients with a GFR <15 mL/min/1.73m^2, the patient should receive as low a dosage as possible, and prompt hemodialysis immediately after the imaging should be considered (17). It is obvious that the standard haemodiaysis protocol of three times a week is insufficient to prevent NSF, as most known cases have developed in such patients. Consequently, the dosage of the haemodialysis should be increased. Most experts recommend a second hemodialysis on the day following the MRI (16, 58). Extending the duration of the haemodialysis can also enhance gadolinium clearance. It is therefore prudent to increase the frequency of the haemodialysis sessions and to prolong their duration (58). As 98.9% of gadodiamide is eliminated after three haemodialysis sessions, an additional one on the third day after the imaging may also be considered (59). It is important to remember that although intensifying haemodialysis after the administration of G-CA is recommended, no hard data is available to prove the effectiveness of this form of treatment in preventing NSF. However, with this approach, most of the gadolinium can be cleared from the body, which might theoretically reduce the risk of developing NSF. Because peritoneal dialysis has a much poorer gadolinium clearance than haemodialysis (24), patients who undergo peritoneal dialysis should also be considered for haemodialysis after the administration of G-CA (58). Alternatively, some authors recommend more frequent exchanges of the peritoneal fluid (16). If G-CA is needed for imaging in patients with kidney failure, a cyclic agent is preferred (60).

Patients with CKD IV

It is not clear how to proceed after the administration of G-CA in patients with a GFR of 15-29 mL/min/1.73m^2. Some centres would perform haemodialysis for those patients who have vascular access. If such access is not established, haemodialysis is generally not recommended in spite of the limited evidence of its benefit. As there is no data from which definite recommendations can be drawn, the decision about how to proceed in such cases has to be made on an individual basis (16, 21, 58). However, for these patients, the administration of G-CA must be looked at critically and should generally be avoided.

Patients with CKD III

The risk of developing NSF after the use of G-CA in patients with a GFR ranging from 30 to 59 mL/min/1.73m^2 remains an open question (17). To date, no haemodialysis is recommended in these cases (21).

Conclusions

NSF is a debilitating disease that affects patients with impaired kidney function. The disease leads to thickening and fibrosing of the skin and frequently involves deeper tissues, such as the inner organs and the locomotor system. Involvement of the latter may lead to contractions, and these, in turn, to disability. Some reports have found increased mortality in NSF patients. There is strong evidence that the disease is caused by the administration of G-CA in patients with kidney failure. However, there may be additional triggers or co-triggers. To date, there is no known effective treatment for NSF, and prevention of the disease is therefore of the utmost importance. G-CA should be avoided in patients with kidney failure, and other imaging modalities should be considered. If the application of G-CA in patients with kidney failure cannot be avoided, haemodialysis immediately thereafter should be considered, depending on the residual kidney function. It should be noted that there is no prove that this approach prevents the development of NSF. If there is no alternative to G-CAs, linear contrast agents should be avoided and cyclic ones, which are more stable, are preferred. However, there are also reports which link the use of cyclic agents to the development of NSF. Peritoneal dialysis is insufficient for eliminating gadolinium from the body after administration during an MRI.

Key facts

- NSF leads to thickening and *fibrosing of the skin*. The disease frequently involves deeper tissues, such as the *inner organs* and the *locomotor system*.
- *Contractions* may lead to the disability of the patient.
- NSF affects patients with *impaired kidney function*.
- There is strong evidence that the disease is caused by the administration of G-CAs, which are given during an *MRI*. There may be additional triggers or co-triggers.
- Currently, there is *no* known *effective treatment*. Therefore, prevention of the disease is of the utmost importance.
- *G-CA should be avoided* in patients with kidney failure.
- If the application of G-CA in patients with kidney failure cannot be avoided, *haemodialysis* should be considered, depending on the residual kidney function. Linear contrast agents should be avoided, and *cyclic* ones should be preferred.
- *Peritoneal dialysis is insufficient* for eliminating gadolinium from the body after its administration during an MRI.

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