Nephrogenic Systemic Fibrosis

Late Skin Manifestations

Nannie Bangsgaard, MD; Peter Marchmann, MD, DMSc; Kristian Rossen, MD; Lone Skov, MD, DMSc

Background: Nephrogenic systemic fibrosis (NSF) is a serious disease that occurs in patients with severe renal disease and is believed to be caused by gadolinium-containing contrast agents. A detailed description of the late skin manifestations of NSF is important to help dermatologists and nephrologists recognize the disease.

Observations: We studied 17 patients with NSF late in the disease. All patients showed epidermal atrophy and hairlessness of the affected regions, primarily the lower legs. Affected areas were symmetrically distributed and hyperpigmented in most cases. Eleven patients showed confluent dermal plaques with thickening and hardening. In contrast, 3 patients presented with wrinkled, redundant skin as seen in cutis laxa. Patients with NSF had significantly poorer scores than control patients on the Daily Life Quality Index (mean [SD], 11.4 [7.4] vs 1.5 [2.3]; P < .001).

Conclusions: This descriptive case series of patients with NSF gives a detailed clinical picture of the skin manifestations late in the disease. It demonstrates that the clinical picture in the late stage has a varied presentation and that NSF has a significant effect on the quality of life.


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Methods:
The Department of Nephrology at Herlev Hospital in Denmark has a large cohort of clinical and histologically verified cases of gadodiamide-related NSF. The cohort, now totaling 28 patients, has been described in recent reports.6,13-16 At the initiation of this study in May 2007, there were 25 patients. Seven patients died and 1 emigrated before the study started. All 17 remaining patients were included. Ten age- and sex-matched patients without NSF who were receiving regular hemodialysis therapy were included as controls.

The study was conducted during October and November 2007 in accordance with the Declaration of Helsinki. Prior approval was obtained from the national Research Ethics Committee, and all patients gave written informed consent before participating.
A single investigator (N.B.) carried out a detailed cutaneous examination of all 17 patients with NSF. Quality of life was assessed by means of the Daily Life Quality Index (DLQI) questionnaire. The DLQI contains 10 questions, each with a score of 1 to 3. The maximum possible score of 30 indicates the worst quality of life. The DLQI has been validated in healthy populations and those with dermatologic conditions for repeatability, internal consistency, and sensitivity to change. 17-19

Blood samples for analysis of PIIIP were collected. The PIIIP levels and DLQI data were analyzed with descriptive statistic measures (mean and SD). Independent-sample t tests were used to compare values for patients with NSF and controls. Tests for normal distribution were done with a probability plot. Equal variance was not assumed. 

RESULTS

The study comprised 17 patients with NSF, 7 women and 10 men between the ages of 35 and 70 years. Baseline characteristics are outlined in the Table. The average interval between the onset of symptoms and clinical examination was 42 months (range, 20-98 months).

### OBJECTIVE SKIN FINDINGS

Skin findings, as observed at the clinical examination, are summarized in the Table. One patient had no current skin abnormalities. In the remaining patients, the skin findings were distributed symmetrically on the extremities. In all patients the lower legs were involved. The clinical

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Time From Onset of Symptoms, mo</th>
<th>Kidney Disease/Current Treatment</th>
<th>Skin Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/40</td>
<td>24</td>
<td>GN/PD</td>
<td>Symmetric, sharply demarcated, confluent dermal plaques of thickened and hardened skin on both lower legs; in same area, atrophy, hair loss, and slight hyperpigmentation, with slack skin appearance</td>
</tr>
<tr>
<td>2/F/70</td>
<td>22</td>
<td>HYP/PD</td>
<td>Symmetric, diffusely demarcated, confluent dermal plaques of thickened and hardened skin on both lower legs; in same area, atrophy, hair loss, and slight hyperpigmentation</td>
</tr>
<tr>
<td>3/M/69</td>
<td>32</td>
<td>GN/HD</td>
<td>No objective findings</td>
</tr>
<tr>
<td>4/F/59</td>
<td>39</td>
<td>PN/HD</td>
<td>Symmetric, diffusely demarcated, confluent dermal plaques of thickened and hardened skin bilaterally on arms and legs; in same area, atrophy, hair loss, hyperkeratosis, and peau d’orange; no hyperpigmentation</td>
</tr>
<tr>
<td>5/M/54</td>
<td>20</td>
<td>GN/PD</td>
<td>Sharply demarcated, confluent dermal plaques of thickened and hardened skin with atrophy and hair loss on both lower legs and right thigh; no hyperpigmentation; symmetric peau d’orange on arms</td>
</tr>
<tr>
<td>6/M/60</td>
<td>28</td>
<td>Medication-induced nephropathy/transplant</td>
<td>Symmetric, diffusely demarcated, confluent dermal plaques of thickened and hardened skin on both lower legs; in same area, atrophy, hair loss, and peau d’orange; no hyperpigmentation</td>
</tr>
<tr>
<td>7/M/67</td>
<td>28</td>
<td>HYP/PD</td>
<td>Symmetric, sharply demarcated, confluent dermal plaques of thickened and hardened skin bilaterally on lower legs, thighs, and fingers; in same area, epidermal atrophy and hair loss; on legs, hyperpigmentation and peau d’orange</td>
</tr>
<tr>
<td>8/M/49</td>
<td>39</td>
<td>GN/HD</td>
<td>Hyperpigmentation sparing only face; widespread atrophy, hair loss, and peau d’orange; only minor areas of diffuse hardening</td>
</tr>
<tr>
<td>9/M/54</td>
<td>30</td>
<td>DM/HD</td>
<td>Diffuse confluent dermal plaques of thickened and hardened skin bilaterally symmetric on arms and legs; in same area, epidermal atrophy and hair loss; arms with hyperpigmentation; legs with areas of erythema and occasionally hyperkeratosis, only minor hyperpigmentation</td>
</tr>
<tr>
<td>10/M/47</td>
<td>55</td>
<td>HYP/HD</td>
<td>Diffuse confluent dermal plaques of thickened and hardened skin, epidermal atrophy, hair loss, and hyperpigmentation bilaterally symmetric on lower legs and hands/fingers</td>
</tr>
<tr>
<td>11/M/68</td>
<td>54</td>
<td>HYP/HD</td>
<td>Diffuse area of atrophy, hair loss, hyperpigmentation, and peau d’orange bilaterally symmetric on lower legs; only minor hardened skin, but areas of slack skin appearance</td>
</tr>
<tr>
<td>12/M/54</td>
<td>71</td>
<td>PCKD/transplant</td>
<td>Diffuse confluent elements of atrophy and hair loss bilaterally symmetric on lower legs; no hardened skin or hyperpigmentation</td>
</tr>
<tr>
<td>13/F/68</td>
<td>43</td>
<td>Nephrocalcinosis/HD</td>
<td>Diffuse confluent dermal plaques of thickened and hardened skin, with epidermal atrophy, hyperpigmentation bilaterally symmetric on lower legs, and hyperkeratosis on both lower legs; in same area, atrophy, hair loss, and peau d’orange</td>
</tr>
<tr>
<td>14/F/50</td>
<td>28</td>
<td>HYP/transplant</td>
<td>Minor confluent elements with atrophy and hair loss bilaterally symmetric distally on arms and legs; no hardened skin; no hyperpigmentation</td>
</tr>
<tr>
<td>15/F/36</td>
<td>28</td>
<td>PN/HD</td>
<td>Diffuse confluent dermal plaques of thickened and hardened skin, epidermal atrophy, hair loss, and hyperpigmentation bilaterally symmetric on lower legs, thighs, and arms; on lower legs, hyperkeratosis and scale</td>
</tr>
<tr>
<td>16/F/43</td>
<td>62</td>
<td>GN/PD</td>
<td>Sharply demarcated areas of erythema, epidermal atrophy, hair loss, and slack skin appearance bilaterally on lower legs and thighs; no hardened skin; no hyperpigmentation</td>
</tr>
<tr>
<td>17/M/35</td>
<td>98</td>
<td>HUN/PD + HD</td>
<td>Diffuse confluent dermal plaques of thickened and hardened skin, with epidermal atrophy, hyperpigmentatio, hair loss, and hyperpigmentation bilaterally symmetric on lower legs and thighs medially; peau d’orange on thigh medially; hyperkeratosis and hyperpigmentation on left arm</td>
</tr>
</tbody>
</table>

Abbreviations: DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HUN, hemolytic uremic nephropathy; HYP, hypertensive nephropathy; PCKD, polycystic kidney disease; PD, peritoneal dialysis; PN, chronic pyelonephritis.
findings were confined to the lower legs in 6 patients and to the lower legs and thighs in 3 patients; in the remaining 7 patients, arms or fingers were also affected.

The superficial skin changes were similar in all patients, but different ends of a spectrum of severity were represented. All 16 currently affected patients showed some degree of epidermal atrophy and loss of hair in the affected areas. Ten of them showed associated hyperpigmentation. Four patients exhibited hyperkeratosis with scaling. Seven patients showed the cobblestone appearance of peau d’orange.

The clinical deep skin changes were more inconsistent. Eleven patients presented with areas of confluent dermal plaques of thickening and hardening, 3 of them with a sharp demarcation to unaffected skin. The remaining 5 patients showed no or only minor dermal hardening. Three of them presented with areas characteristic of cutis laxa, with the skin appearing inelastic and redundant and hanging in loose, pendulous folds. There was a wide range of severity in these patients. Patient 16 presented with widespread bilateral, symmetrically distributed, sharply demarcated areas involving the lower legs and thighs. At the opposite end of the spectrum, patient 14 presented with only small but sharply demarcated affected areas distally on the arms and legs with slight atrophy and loss of hair. Patient 1 had a mixed clinical presentation of both deep hardening and wrinkled, redundant skin. Examples of the 2 different dermal manifestations, hardening and wrinkled redundant skin, are shown in Figure 1.

**DLQI SCORES**

Fifteen patients and 10 controls completed the DLQI questionnaire. The 2 patients who did not complete the questionnaire were very ill and hospitalized.

Scores are summarized in Figure 2. The DLQI mean score was 11.4 (7.4), i.e., markedly impaired with scores similar to those with severe dermatologic disease. The high scores were mainly due to restrictions in activity, with most problems reported in questions 3 (house activities), 5 (social/leisure activities), and 6 (sports). In contrast, the scores for controls were significant lower, with a mean of 1.5 (2.3) (P < .001).

**PIIIP LEVELS AND HISTOLOGIC FINDINGS**

The patients with NSF had a mean PIIIP level of 12.9 (6.6) µg/L, statistically significantly higher than the mean value for controls of 7.6 (2.6) µg/L (P = .01). Three patients (patients 8, 9, and 15) had a PIIIP level higher than 20 µg/L. These 3 patients were severely affected by the disease, with contractures and reports of weakness and pain; patients 9 and 15 were confined to wheelchairs.

In all patients the diagnosis of NSF had previously been histologically confirmed according to criteria defined by Cowper et al. In 5 patients we were able to analyze biopsy specimens collected during early and late stages of the disease. In all 5 patients fibrosis was present in the late biopsy specimen. In 2 patients the fibrosis was worse than in the early stage, and in 3 patients the fibrosis was less prominent than in the early stage. In patient 3, who seemed clinically unaffected, fibrosis was present in the subcutis. In patients 1, 11, and 16, who clinically presented with loose skin, the histologic finding was a marked reduction of elastic fibers at all levels of the skin combined with different degrees of fibrosis. The loss of elastic fibers for all 3 patients was more prominent in the biopsy specimens collected late in the disease, supporting the clinical course seen in these patients.

**COMMENT**

This descriptive case series gives a detailed clinical picture of the late skin manifestations in patients with NSF. The skin manifestations seen at the onset of symptoms and in the early stage of the disease have been described, with edema, erythema, and warmth being present in addition to the fibrosis in the affected area. The skin changes described in our patients late in the disease are different, with a clinically stationary picture of symmetrically distributed areas of various degrees of epidermal atrophy and hair loss. In most cases these findings were combined with confluent dermal plaques of...
thickening and hardening, but in a few patients they were noted along with wrinkled, redundant skin, as seen in cutis laxa.

It is important to recognize that NSF in the late stage of the disease can present without the typically described hardening of fibrosis but with the appearance of wrinkled, redundant skin. This late manifestation has previously been described in a 26-year-old white man with end-stage renal disease, who initially presented with the characteristic changes of thickening. Findings in a skin biopsy specimen were representative of NSF. During the following 2 years, the skin manifestations changed to wrinkled, redundant skin, and a skin biopsy specimen disclosed the thickening of collagen together with elastolysis in the dermis. This clinical and histologic manifestation was present in 3 of our patients. None of these patients had contractures. It is worth noting that these patients also had a reduced quality of life and reported pain, weakness, and restricted activity related to the affected areas.

The skin changes described for the patients with NSF, including thickened, hardened skin with hyperpigmentation and occasional flexion contractures, are characteristic of other fibrosing disorders. Our cases, however, demonstrated the clinical and histologic features that distinguish NSF from other similar fibrosing disorders, such as scleromyxedema and morphea/scleroderma. Our patients with NSF showed an acral distribution of the lesions and involvement of lower rather than upper limbs. Morphea/scleroderma usually begins on the trunk and subsequently spreads to involve the limbs. In classic scleromyxedema the head and neck are usually also involved. These areas were not affected in any of our patients.

We have seen extremely high levels of PIIIP in a few patients with NSF early in the disease. Under normal circumstances the collagen level remains constant except during active fibrosis. Among the different procollagens found in humans, PIIIP is one of the most abundant. Serum PIIIP level has been established to reflect the degree of tissue fibrosis in various fibrotic diseases and is used routinely to evaluate liver fibrosis in patients with psoriasis treated with methotrexate. Elevated PIIIP levels have been reported in patients with renal failure; values have been moderate and without correlation to renal function. Accordingly, the range of PIIIP in our controls was higher than that seen in a normal population. The PIIIP range in our patients in the late stage of disease was significantly higher than that for controls. There appears to be a correlation between PIIIP level and severity of disease, with severe cases being associated with higher concentrations. This was not statistically evaluated. It may be that PIIIP is an indicative marker for still-active disease in patients with NSF.

The results of the DLQI questionnaire showed significantly impaired quality of life. Scores were similar to those with severe dermatologic diseases, such as psoriasis, indicating a considerable effect on patients' lives. Compared with controls, patients with NSF scored significantly higher on the DLQI. If data from the 2 severely affected hospitalized patients had been available, we expect the difference would have been even higher.

The high scores are mainly due to restrictions in activity, with most problems reported in questions 3 (house activities), 5 (social/leisure activities), and 6 (sports).

In conclusion, this descriptive case series has demonstrated the cutaneous manifestations in NSF late in the disease to be different from those seen early in the disease and to have a varied presentation. In addition, the study has proved NSF to have a significant effect on the quality of life.

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Author Contributions: Drs Bangsgaard, Marckmann, and Skov had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bangsgaard, Marckmann, and Skov. Acquisition of data: Bangsgaard and Skov. Analysis and interpretation of data: All authors. Drafting of the manuscript: Bangsgaard and Skov. Critical review of the manuscript for important intellectual content: All authors. Statistical analysis: Bangsgaard. Administrative, technical, and material support: Bangsgaard and Skov. Study supervision: Marckmann and Skov.

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REFERENCES

William Byrd on Ticks, 1728

William Byrd (1674-1744) was a Virginia aristocrat who, like many of his countrymen, was sent to England as a boy to complete his education. A keen amateur naturalist, he was elected a Fellow of the Royal Society when he was 22 years old (his first paper read before the society was, interestingly, a description of vitiligo).1 He returned to Virginia in 1696 and settled down to manage his plantation, Westover. In 1728, he led an expedition to survey the boundary line between the colonies of Virginia and North Carolina.2 As the survey party hacked its way through a wilderness of swamps, swift-flowing rivers, and impenetrable hardwood forest, he busily recorded the details of the natural phenomena they encountered. Amid his observations concerning bears, rattlesnakes, beavers, medicinal plants, and native peoples, he also discussed some of the smaller fauna of the border country.

“The ticks are either deer ticks or those that annoy the cattle. The first kind are long and take a very strong gripe, being most in remote woods above the habitations. The other are round and more gently insinuate themselves into the flesh, being in all places where cattle are frequent.”3 Byrd goes on to describe the tick-repelling effects of the juice of pennyroyal (Mentha pulegium) and then states, “A strong decoction of this is likewise the most effectual remedy against seed ticks, which bury themselves in your legs when they are so small you can hardly discern them without a microscope.”

Byrd’s simple observations are noteworthy for 2 reasons. First, they are very likely the earliest scientific descriptions of North American ticks, made doubly interesting by his careful differentiation between the deer tick and the rounder, less tenacious American dog tick, Dermacentor variabilis. Byrd’s deer tick was probably Ixodes scapularis but could conceivably have been the lone star tick, Amblyomma americanum, which is also found—at least nowadays—in the area of Virginia through which Byrd traveled.4 The tiny “seed ticks” were, of course, the nymphal phase of Ixodes ticks. The second reason that Byrd’s commentary is notable is his mention of the microscope. In 1728, microscopes were rare indeed, particularly in the woods of the American colonies. By mentioning the microscope, Byrd is actually showing off to impress his intended readers, the gentlemen of the Royal Society.

Two hundred years after Byrd’s observations, the first scientific studies of deer tick population biology began. Fifty-five more years would pass before Lyme disease and its transmission by Ixodes was described and our understanding of what makes deer ticks tick was fairly complete. But in his small way, William Byrd started it all.

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