Nephrogenic systemic fibrosis (NSF) was first documented in 1997 in an international registry. It was initially known as nephrogenic fibrosing dermopathy because of its characteristic thickening and hardening of skin, but due to the various other organ systems that it can affect, the name was changed to NSF. The diagnosis of NSF is based on clinicopathological guidelines reported in 2011 by Girard et al.2

The first reports of the disease correlated with the initial use of gadolinium as a contrast agent for magnetic resonance angiography in patients with renal failure.1 Approximately 380 cases of NSF have been documented in the International Nephrogenic Systemic Fibrosis Registry, with a marked increase in incidence until 2006, when the relationship between gadolinium exposure and NSF was recognized. In 2010, the US Food and Drug Administration published guidelines and black box warnings recommending avoidance of gadolinium-containing contrast agents in patients with kidney failure.3

The clinical history and histopathological features of this case support the diagnosis of NSF 10 years after exposure to gadolinium. Although the use of gadolinium contrast agents in patients with kidney failure has markedly decreased, patients with exposure to gadolinium years to decades previously may manifest the disease.

Report of a Case
A man in his 50s receiving chronic hemodialysis during the past 25 years for end-stage renal disease secondary to focal segmental glomerulosclerosis was seen at our clinic with recent-onset extensive papular eruption on his body and 2 new dermal plaques on his right arm. The skin lesions had first developed in June 2014, shortly after the patient had undergone fistulography using iohexol contrast. The fistulogram showed narrowing of the patient’s brachial artery-transposed basilica vein fistula but no obstruction or clot. The patient demonstrated no itching, decrease in range of motion, or hardening of the skin at that time.

Physical examination revealed a widespread eruption of dermal papules 4 to 5 mm in diameter producing linear ar...
rays on the neck, back, chest, abdomen, and thighs without sclerosis (Figure 1). The right volar forearm had 2 indurated dermal plaques in the vicinity of the arteriovenous fistula. Microscopic examination of a punch biopsy specimen of a characteristic papule on the patient’s neck revealed thickening of dermal collagen with an increase in spindle cells and dermal mucin (Figure 2). The fibroblast-like spindle cells stained positive with a CD34 immunostain (Figure 3A), and the mucin highlighted with a colloidal iron stain (Figure 3B). Discussion with the patient and review of his medical record revealed prior exposures to gadolinium-containing contrast several times between 1998 and 2004 during magnetic resonance angiography of the abdomen, as well as several fistulograms. After 2004, the patient had received no gadolinium-containing contrast.

Discussion

Nephrogenic systemic fibrosis is included in the differential diagnosis of scleroderma-like disorders that affect the skin and internal organs. In 2007, High et al first reported the presence of gadolinium in skin affected by NSF as measured by electron microscopy with energy-dispersive spectroscopy. In 2010, the US Food and Drug Administration stated that 3 contrast agents (gadopentetate dimeglumine, gadodiamide, and gadoversetamide) were contraindicated in patients with acute or chronic kidney disease. Although gadolinium has been found in the skin of affected individuals, the mechanism by which fibrosis develops is unknown to date. One hypothesis proposes that infiltrating CD68+/XIIIa+ dendritic cells synthesize transforming growth factor β, a profibrotic cytokine. Another hypothesis suggests that bone marrow–derived CD45RO+/CD34+/collagen I+ circulating fibrocytes are recruited to the skin, which produce collagen and resulting fibrosis. Cowper1 found that almost all patients with NSF relate their disease onset to a recent surgical procedure or thrombotic event, suggesting that tissue or vascular injury may be an important component in the initiation of the disease.7

Nephrogenic systemic fibrosis is most common in middle-aged adults but has been described in children and the elderly. It manifests as patterned, thick, indurated plaques in a symmetric distribution on the extremities and trunk. The
plaques can vary from erythematous to hypopigmented and can have an irregular, advancing edge with an amoeboid appearance. The extremities can develop joint contractures, leading to pain and loss of mobility. Patients can also be seen with yellow scleral plaques and systemic fibrosis affecting lungs, heart, and skeletal muscle.8 The differential diagnosis of NSF includes scleromyxedema, eosinophilic fasciitis, lipodermatosclerosis, scleroderma/deep morphea, eosinophilia-myalgia syndrome, and chronic graft-vs-host disease.1

The histopathology of NSF resembles scleromyxedema, with features that include thickened collagen bundles and increased dermal fibroblast-like cells that stain positive for CD34 and procollagen I. Vascular proliferation, mucin deposition, and an increased number of dendritic cells can be observed.9 However, the presence of subcutaneous involvement in NSF may be a distinguishing feature.10 In addition, patients with scleromyxedema have a distinct clinical presentation of numerous minute papules in linear arrays, often involving the face, which is spared in NSF. Due to the difficulties in distinguishing NSF and scleromyxedema on histology alone, a thorough clinical history and physical examination are necessary.

Girardiet al2 proposed clinical and histopathological criteria for NSF using data from the Yale International Nephrogenic Systemic Fibrosis Registry. Of these major clinical criteria, our patient was seen with clinical findings of patterned plaques. Of the minor clinical criteria, dermal papules, superficial plaques, and patches were present. Of the histological criteria, increased dermal cellularity, CD34+ cells with tram tracking, collagen bundles, and preserved elastic fibers were present.

Table 1. Clinical Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Scenario</th>
<th>Clinical Interpretation</th>
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</thead>
<tbody>
<tr>
<td>4</td>
<td>&gt;1 Major criteria</td>
<td>Highly consistent with NSF</td>
</tr>
<tr>
<td>3</td>
<td>1 Major criterion</td>
<td>Consistent with NSF</td>
</tr>
<tr>
<td>2</td>
<td>≥1 Minor criteria</td>
<td>Suggestive of NSF</td>
</tr>
<tr>
<td>1</td>
<td>≤1 Minor criterion</td>
<td>Inconsistent with NSF</td>
</tr>
<tr>
<td>0</td>
<td>Diagnostic of another entity</td>
<td>NSF excluded</td>
</tr>
</tbody>
</table>

Abbreviation: NSF, nephrogenic systemic fibrosis.

Box. Clinicopathological Criteria

Clinical Findings: Major Criteria
- Patterned plaques
- Joint contractures
- Cobblestoning
- Marked induration/peau d'orange

Clinical Findings: Minor Criteria
- Puckering/linear banding
- Superficial plaque/patch
- Dermal papules
- Scleral plaques (age <45 y)

Histological Findings
- Increased dermal cellularity (score +1)
- CD34+ cells with tram tracking (score +1)
- Thick and thin collagen bundles (score +1)
- Preserved elastic fibers (score −1 if absent)
- Septal involvement (score +1)
- Osseous metaplasia (score +3)
Table 2. Histopathological Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Histological Interpretation</th>
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<tbody>
<tr>
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Abbreviation: NSF, nephrogenic systemic fibrosis.

This led to a clinical score and a histopathological score that were consistent with NSF (Box, Table 1, and Table 2).2

There have been anecdotal reports of improvement of NSF lesions after treatment with extracorporeal photopheresis, sodium thiosulfate, and pentoxifylline. Glucocorticoids, plasmapheresis, intravenous immunoglobulin, cyclophosphamide, thalidomide, intraleisional interferon alpha, and topical calcipotriene therapies have had limited success. Optimization of renal function through medical therapy or transplantation appears to be effective in some cases. Physical and occupational therapy referral to maintain joint mobility is critical.11,12 Most recently, Swaminathan et al13 found that NSF-confirmed tissue expressed phosphor-70-ribosomal-S6, a protein downstream of the phosphoinositol-3-kinase and rapamycin pathways. Rapamycin is an inhibitor of phosphor-70-ribosomal-S6 directly and the 2 aforementioned pathways. Swaminathan et al reported rapid clinical resolution of NSF skin manifestations, including edema and pain in the lower extremities, with rapamycin treatment, although their results have not been duplicated to date. Avoidance of gadolinium-based contrast agents in patients with renal failure is the most effective means of preventing NSF.

Conclusions

The time course from exposure to gadolinium to the presentation of NSF was documented from weeks to 10 years in the case reported herein. All patients with symptoms of a fibrosing dermatopathy and history of kidney failure should undergo testing for NSF regardless of the number of years since last gadolinium exposure.

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Study concept and design: Larson, Gagnon, Cropley.
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REFERENCES