

A case of nephrogenic fibrosing dermopathy/ nephrogenic systemic fibrosis

Andrew S Weiss, M Scott Lucia and Isaac Teitelbaum*

SUMMARY

Background A 61-year-old female with end-stage renal disease who was undergoing hemodialysis presented with an 8-week history of upper and lower extremity weakness associated with skin tightness and contractures.

Investigations Physical examination, blood analysis, electromyogram and skin biopsy.

Diagnosis Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis.

Management Methylprednisolone, thalidomide and physical therapy.

KEYWORDS circulating fibrocytes, nephrogenic fibrosing dermopathy, nephrogenic systemic fibrosis

CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 61-year-old white female with end-stage renal disease (ESRD) was transferred from another hospital for evaluation of upper and lower extremity weakness in association with skin tightness and contractures. The patient's symptoms had started 8 weeks before presentation, soon after she had received an influenza vaccination. Weakness was associated with firmness and tightening of the skin, followed by development of contractures. Eleven days before transfer to our center, the patient had presented to another hospital complaining of chest pain and dyspnea. A CT angiogram of the chest performed with 150 ml of iohexol (Omnipaque®, GE Healthcare, Oslo, Norway) contrast had revealed a pulmonary embolus, and anticoagulation had been initiated.

The patient's past medical history was notable for ESRD, which was thought to be secondary to obstructive uropathy from recurrent nephrolithiasis. She had started hemodialysis 6 months before presentation. Additional past medical history included morbid obesity (for which she had undergone intestinal bypass surgery in 1974), seronegative polyarticular arthritis (thought to be secondary to her intestinal bypass), degenerative joint disease, hypertension and hypothyroidism. She also suffered from mild expressive aphasia as a result of post-traumatic brain injury from a motor vehicle accident 13 years earlier.

The patient's medications upon transfer from the other hospital included metoclopramide, lansoprazole, sertraline, cyclobenzaprine, oxycodone, diazepam, sevelamer, midodrine (administered predialysis), erythropoietin, warfarin, levothyroxine, tetracycline, transdermal lidocaine, multivitamins (Nephro-Vite®, R & D Laboratories, Marina del Ray, CA, USA) and docusate sodium. She had also been initiated on high-dose steroids (500 mg

AS Weiss is a Fellow in the Division of Renal Diseases and Hypertension, MS Lucia is an Associate Professor of Pathology, and I Teitelbaum is a Professor in the Division of Renal Diseases and Hypertension at the University of Colorado Health Sciences Center, Denver, CO, USA.

Correspondence

*University of Colorado Health Sciences Center, Division of Renal Diseases and Hypertension, 4200 East Ninth Avenue, C281, Denver, CO 80262, USA
isaac.teitelbaum@uchsc.edu

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Figure 1 Skin thickening, tightness and contractures are hallmarks of the clinical findings in nephrogenic fibrosing dermopathy.

intravenous methylprednisolone twice daily) for a presumed autoimmune disorder before transfer to our hospital.

On physical examination, the patient appeared chronically ill and was afebrile. Her blood pressure was 128/74 mmHg and her pulse rate was 96 beats per minute. Her oxygen saturation level was 96% on room air. A tunneled hemodialysis catheter was noted in the right internal jugular vein. Dermatologic examination revealed diffuse

nonerythematous thickening and tightening of the skin over the abdomen, arms and legs, sparing the chest and face. She had grade 2+ pitting pretibial lower extremity edema. Her musculoskeletal examination was notable for bilateral contractures of the upper and lower extremities with an extremely limited range of motion involving the shoulders, elbows, wrists, hips, knees and ankles (Figure 1). She also exhibited significant pain upon movement of these joints.

Laboratory values at admission are shown in Table 1. The results of tests for antinuclear antibody, complement components C3 and C4, anti-Scl-70 (antitopoisomerase I antibody), anti-SSA (anti-Sjögren's syndrome A antibody), anticentromere antibody, serum protein electrophoresis, thyroid-stimulating hormone, troponin I, creatine phosphokinase, aldolase, vitamin B₁₂, folate, and antibodies against cardiolipin, β₂ glycoprotein, endomysium and gliadin were all negative or within normal limits. An electromyogram (a test that measures the electrical activity of muscles) of the lower extremities was also unremarkable.

A 6 mm punch biopsy was performed on the left thigh. Sections of skin from the left thigh showed keratinizing, slightly atrophic stratified squamous epithelium with an underlying superficial dermis, which was relatively unremarkable. The subcutaneous tissue, however, showed broad bands of fibrosis intersecting in a haphazard fashion between lobules of mature adipose tissue without a significant inflammatory component (Figure 2). No significant cytologic atypia or mitotic figures were identified. A CD34 immunostain was positive in scattered dendritic cells (Figure 3). Procollagen staining was not performed. These biopsy results were interpreted as being consistent with a diagnosis of nephrogenic fibrosing dermopathy (NFD).

The patient underwent extensive physical therapy and was eventually discharged to a rehabilitation facility. She was on a steroid taper at discharge and there were plans to initiate her on thalidomide 100 mg daily as an outpatient. Within weeks of her discharge, however, she died of respiratory failure at another hospital; the cause of death was presumed to be aspiration pneumonia.

DISCUSSION OF DIAGNOSIS

The initial description of NFD was published in 2000 as a case series of 15 patients who developed skin hardening, thickening and hyperpigmentation localized to the extremities.¹ The unifying

Table 1 Patient's laboratory values on admission.

Laboratory parameter	Value
Serum sodium	131 mmol/l
Serum potassium	5.2 mmol/l
Serum bicarbonate	20 mmol/l
Serum creatinine	203 μmol/l (2.3 mg/dl)
Serum calcium	2.3 mmol/l (9.1 mg/dl)
Serum magnesium	0.7 mmol/l (1.8 mg/dl)
Serum phosphorus	1.3 mmol/l (4.0 mg/dl)
White blood cell count	11,700/ml 76% neutrophils 13% monocytes 11% lymphocytes 0% band cells 0% eosinophils 0% basophils
INR	2.92
Hematocrit	36%
Platelet count	350,000/mm ³
Westergren sedimentation rate	64 mm/h
Total protein	52 g/l (5.2 g/dl)
Serum albumin	21 g/l (2.1 g/dl)

Abbreviation: INR, international normalized ratio.

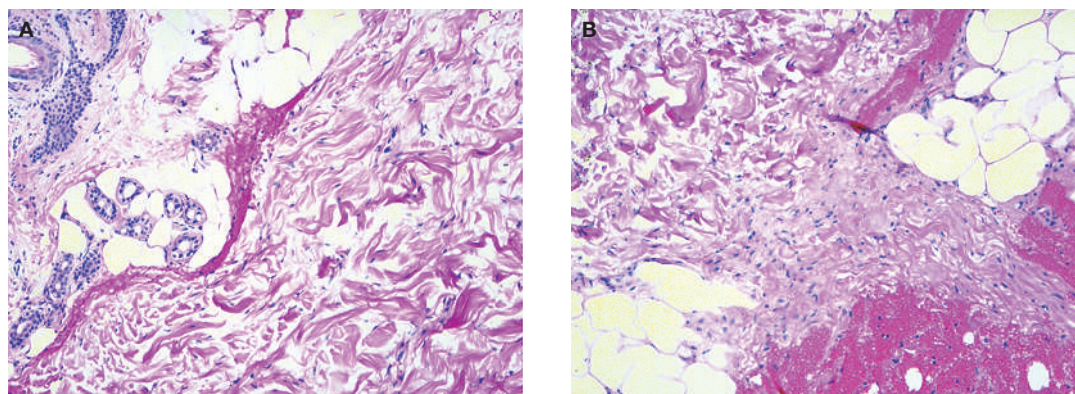


Figure 2 Punch biopsy slides of left thigh (hematoxylin and eosin stain; magnification $\times 100$) showing widening of subcutaneous septae with thick collagen bundles in (A) the deep dermis and (B) the subcutaneum.

characteristic of these patients was that all had received a form of renal replacement therapy before diagnosis. Since the initial characterization, over 175 cases have been reported and it now seems that renal dysfunction, with or without renal replacement therapy, predisposes patients to this disease.² The manifestations of NFD were initially thought to be confined to the skin; however, recent reports reveal systemic fibrosis on autopsy including skeletal muscles, diaphragm, pleura, pericardium, myocardium, dura mater and vessels of the heart.^{3–6} This newly described systemic involvement prompted the name of the disease to be changed to nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis (NFD/NSF).

Definitive diagnosis of NFD/NSF is made by full-thickness skin biopsy at the involved site. Characteristic histological findings include thickened reticular dermal collagen bundles with dermal spindle cells that stain positive for both CD34 and procollagen.⁷ These spindle cells are thought to have the immunophenotype of 'circulating fibrocytes', which are characterized as circulating cells of bone marrow origin that express markers of both connective tissue cells and circulating leukocytes.⁸ Extensive mucin deposition is often seen between collagen bundles, but in contrast to other fibrosing disease states, inflammatory cells are usually absent.⁹ Although the etiology has yet to be elucidated, it seems that some antigenic stimulus associated with renal dysfunction upregulates these circulating fibrocytes and induces an aberrant form of wound healing.

Although no mechanisms have been established to account for this upregulation, several correlations

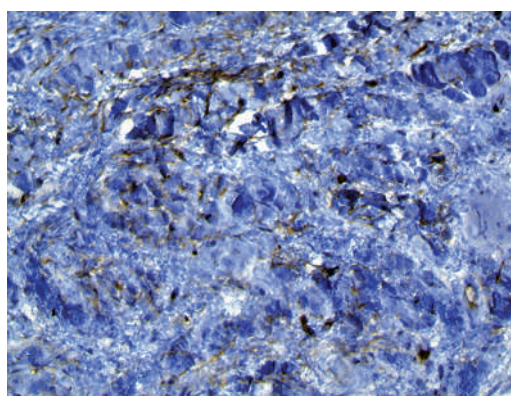


Figure 3 Punch biopsy slide of left thigh showing positivity in dendritic cells (CD34 stain, hematoxylin counterstain; magnification $\times 200$).

have been observed. First, like our patient, over 10% of individuals with NFD/NSF present with a thrombotic event or hypercoagulable state.^{7,10} Another case series indicated that lack of angiotensin-converting-enzyme inhibitor use can predispose patients to NFD/NSF because the profibrotic effect of transforming growth factor β is not inhibited.¹¹ High doses of erythropoietin have also been postulated as a contributing factor for fibrosis.¹²

Recently, a case series reported a connection between NFD/NSF and a gadolinium-containing contrast agent used for magnetic resonance angiography (MRA) in patients with ESRD and documented metabolic acidosis.¹³ After learning of 25 cases of NFD/NSF in patients with renal failure who underwent MRA with gadolinium-containing contrast agents, the US FDA issued a public health advisory on 8 June 2006. Although

Box 1 Differential diagnoses for nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis.

- Scleromyxedema
- Systemic sclerosis
- Eosinophilic fasciitis
- Pretibial myxedema
- Eosinophilia–myalgia syndrome
- Spanish toxic oil syndrome

no direct link has been made between gadolinium-containing contrast agents and NFD/NSF, the FDA has asked physicians to use caution when ordering MRA with gadolinium-containing contrast in patients with advanced renal failure (i.e. those already on dialysis or with a glomerular filtration rate of ≤ 15 ml/min).¹⁴ While the patient did receive 150 ml of nonionic iodinated contrast for a CT angiogram of the chest at an outside institution, we found no evidence of gadolinium exposure in the weeks leading up to her transfer to our hospital. We could not, however, verify whether she had received gadolinium in the 6 months before presentation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for NFD/NSF includes a number of other fibrosing disorders, which are listed in Box 1. These diseases and their characteristic clinical and histopathologic findings have been well detailed in previous NFD/NSF case reports.^{9,15}

Unlike patients with scleromyxedema, in whom skin thickening can occur on the head, neck, arms and upper trunk, our patient exhibited skin thickening predominantly on the extremities and abdomen, sparing the face and neck. Lack of inflammatory cells and myxoid stroma on the biopsy is uncharacteristic of scleromyxedema. The absence of a monoclonal pattern on serum protein electrophoresis also helped to rule out this disease process. With regard to systemic sclerosis, negative results for antinuclear, anticentromere and anti-Scl-70 antibodies as well as a lack of dermal and perivascular inflammation on the biopsy made this diagnosis highly unlikely. Pretibial myxedema can be seen in patients with Graves' disease, but a normal thyroid-stimulating hormone level and the lack of other clinical manifestations

of hyperthyroidism made this diagnosis unlikely. Eosinophilic fasciitis, as its name implies, is characterized by peripheral eosinophilia, hypergammaglobulinemia and dermal inflammation on biopsy. Indurated skin changes typically involve the extremities, trunk and neck, but spare the feet and hands. Our patient had no evidence of peripheral eosinophilia or dermal inflammation on biopsy, and physical examination revealed both hand and foot involvement. Eosinophilia–myalgia syndrome and Spanish toxic oil syndrome have been associated with ingestion of toxins from contaminated L-tryptophan and contaminated cooking oil, respectively. Both disease states are associated with marked peripheral eosinophilia, myalgia and an inflammatory infiltrate seen on skin biopsy. Our patient had none of these findings.

DISCUSSION OF TREATMENT

Many different treatment options have been explored for NFD/NSF, with varying degrees of success. No single treatment has been proven effective; however, improvement in renal function seems to halt or reverse the process. Therapeutic approaches that have shown promise include steroids, plasmapheresis, extracorporeal photopheresis, intravenous immunoglobulin, ultraviolet light therapy, physical therapy, thalidomide, renal transplantation and, most recently, pentoxifylline.¹⁶

CONCLUSION

NFD/NSF is a newly characterized disease that is found only in patients with renal dysfunction. The fibrosis seems to be triggered by an unknown antigenic stimulus that causes the migration of bone-marrow-derived 'circulating fibrocytes' to the skin and other systemic locations and the promotion of fibrotic changes similar to those that occur during wound healing. As NFD/NSF is a progressive disease, it is far from certain whether the proposed treatment modalities are effective. Clinicians and patients should refer to the official NFD/NSF website¹⁶ for the latest information on diagnosis and management of this disease.

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Competing interests

The authors declared they have no competing interests.