

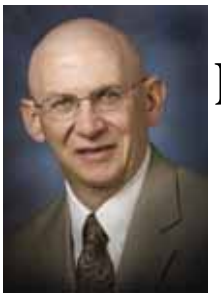

Nephrogenic Systemic Fibrosis – A Clinical and Pathologic Perspective

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INTRODUCTION

Nephrogenic Systemic Fibrosis (NSF), an initially obscure fibrosing condition, has been recognized and defined over the past ten years in patients with Acute Kidney Injury (AKI) and advanced Chronic Kidney Disease (CKD, stage 4 & 5). Starting in the late 1990s, we have cared for a patient at Lancaster General Hospital who illustrates many of NSF's clinical and historical features, and who, in retrospect, has a confirmatory pathologic diagnosis of NSF.

CASE REPORT

A 50-year-old white female with Polycystic Kidney Disease and End Stage (Stage 5) CKD, was transferred to the Lancaster General Dialysis Unit in February 1996 after an unsuccessful kidney transplant. She had been on peritoneal dialysis since the early 1990s, but had required hemodialysis post-transplant due to an abdominal abscess and an open abdominal wound.

This unfortunate patient's subsequent course on hemodialysis was complicated by thrombotic problems with dialysis access. Her surgical history was significant for the placement of 4 cuffed dialysis catheters and later arteriovenous grafts (AVGs) in both arms and the left groin. She had 5 subsequent surgical thrombectomies and AVG revisions. She also underwent 28 angiographic interventions for clotted AVGs during her 9 years at Lancaster General Hospital. Anti-Cardiolipin antibodies, ANA, and workup for other coagulopathies were negative.

She had allergies to Latex and intravenous contrast material, and received a steroid prep prior to angiographic procedures. During her protracted illness, only one episode is recorded during which she received Gadolinium (Gd) – for an MRI of the brain in November 1997 (Gadopentetate dimeglumine [Magnevist] 17 cc or 0.1 mmol Gd/kg body weight).

Soon after transfer to LGH, the patient complained of pruritus, and in August 1996 she developed a rash described as hives. A skin biopsy of the right forearm showed a slight increase in "mast cell density," and she received some relief from Prednisone 20 mg daily for 9 days. By August 1997 she complained of restless legs and numbness in the toes and feet, and electromyography confirmed a diagnosis of neuropathy.

In 1998 her intestine was perforated during a routine colonoscopy, and she required a colostomy that could not be reversed due to her fragile tissues. The colostomy also prevented her from being listed for a kidney transplant.

In the spring of 2000, she complained of pain, swelling, and morning stiffness in multiple joints, and a consulting rheumatologist started her on Prednisone for a "symmetrical polyarthritis." In December 2000, she began to complain of "hardening" in her legs, especially her calves, and an area with a woody indurated texture extended from her lower legs to the groin. The rheumatologist proposed a diagnosis of Eosinophilic Fasciitis and requested a skin biopsy. An excisional biopsy of the skin, subcutaneous tissue, fascia, and muscle of the right thigh was interpreted by an outside dermatopathologist as indicating Scleroderma. A subsequent review of the biopsy at a different institution yielded a diagnosis of Septal Panniculitis with multifocal palisaded granulomatous inflammation.

Over the next seven months her symptoms progressed, as skin changes from her calves and thighs also moved to her buttocks. She was referred to a Scleroderma clinic, where the diagnosis of Scleroderma was questioned due to the absence of Raynaud's Phenomena and negative anticentromere and anti-Scl 70 antibodies. An alternative diagnosis of "Eosinophilic Fasciitis" was proposed, and she was placed on CellCept.

In November 2002 she was readmitted with complaints of severe refractory pain, inability to walk, and increasing stiffness in her joints that hindered her ability to eat. The induration of her skin had progressed from her legs to her upper extremities. She was again placed on Prednisone as the CellCept did not relieve her symptoms.

About this time she developed apparent changes of Calciphylaxis. She had a large, crusted erosion with an overlying black eschar on her right lateral calf, and black painful lesions on her fingers and toes. Her parathyroid level was 4370 pg/mL (normal 150-300 pg/mL). She underwent a parathyroidectomy in October 2003 with resolution of all the ischemic lesions.

She continued on Prednisone and appeared to tolerate her pain and other somatic complaints. Her extremities were still tight, but she had no rashes and was able to walk again. In 2003 she also underwent cardiac catheterization and a pacemaker/defibrillator was inserted. Toward the end of July 2004, she was rushed to the emergency room in shock with a large amount of blood in her colostomy. This long-suffering woman was not thought to be a candidate for surgical intervention, and she died with a presumed small bowel infarction.

PATHOLOGY REVIEW*

Sections of the skin taken from the right thigh in March 2001 demonstrated variable changes. Some foci showed only mild thickening of the dermis with mild septal thickening within the panniculus, composed of a subtle increase in bipolar spindle cells within a mildly myxoid matrix. In other foci there was more prominent thickening of dermal collagen with extension into the subcutaneous lobules. In these areas, a proliferation of cells with oval and bipolar nuclei was seen, as well as a few multinucleated cells. The collagen was deeply eosinophilic with marked clefting. Patchy foci in these areas showed mild myxoid changes. There were also multiple foci of collagen degeneration with calcification and surrounding giant cell reaction. There was minimal inflammation. Immunohistochemical staining revealed an increased number of CD-34 positive spindle cells with elongated dendritic processes, as has been previously described in NSF.

Sections of the bowel segment removed in 1998 when she had surgery for a perforated intestine showed exaggerated cellular fibroblastic proliferation within the bowel wall.

*Pathologic diagnosis confirmed by Dr. Shawn Cowper, NSF Registry/Yale school of Medicine – personal communication L.E.C.

DISCUSSION

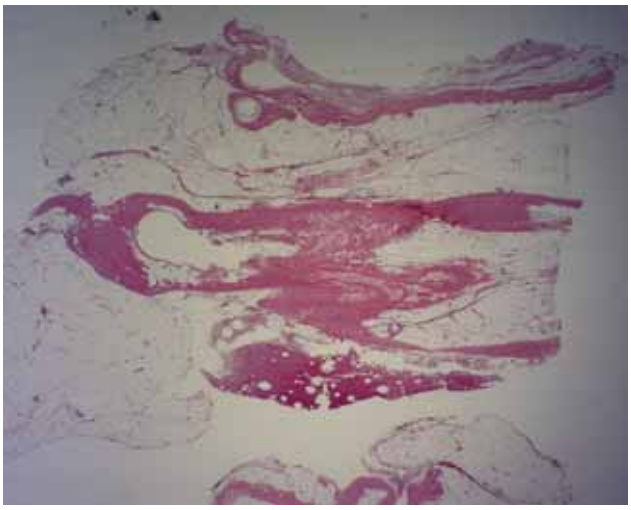
The pathologic findings support a diagnosis of Nephrogenic Systemic Fibrosis (NSF). The patient's clinical course was consistent with NSF, but the confirmation of the biopsy was required to secure the diagnosis.

In the original case reports, many patients had thrombotic episodes, associated anti-Cardiolipin Antibodies, and repeated surgical or angiographic procedures. A "triggering event" was postulated,[1] but was only recently traced to exposure to Gadolinium (Gd) during MRI/MRAs.[2] (See Leslie's accompanying article entitled "Nephrogenic Systemic Fibrosis: A Radiology Perspective" in Imaging Insights.)

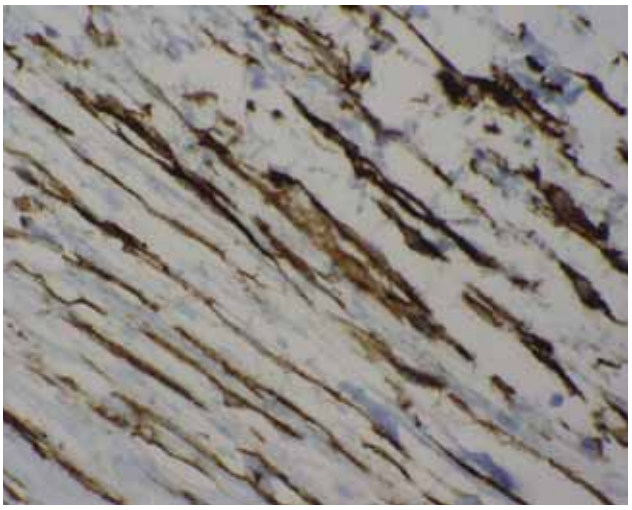
Our patient certainly had many thrombotic episodes during her 9 years on hemodialysis. She did have at least one exposure to Gd, although it wasn't until 4-5 years later that the classic symmetrical, lower extremity changes in her skin were appreciated. The reported latency between Gd exposure and skin changes has usually been only 2-4 weeks, though one report described a delay of 18 months.[3] The delay in recognizing our patient's NSF may have been due to our lack of knowledge in the late 1990s or possibly due to a later use of Gd in the Angiography Suite or Cardiac Catheterization Laboratory that our chart review failed to reveal.

Our patient's complaints of itching, joint pain, and skin changes are typical of the described cases of NSF. The skin is bound down and has a "woody" texture ('peau d'orange'). The changes start in the legs symmetrically but can progress to the upper extremities and torso. The face is usually spared but scleral yellow "plaques" have been described.[4] Also, bullae have been described in the hands and feet.[5]

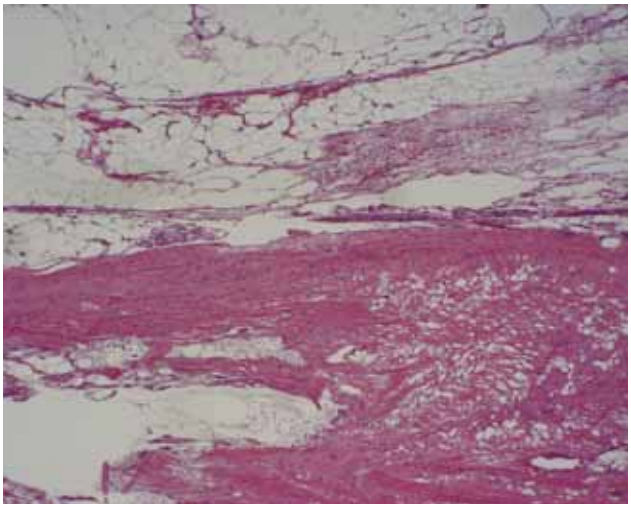
Initial reports called the above changes "Nephrogenic Fibrosing Dermopathy" (NFD) but subsequent case studies confirmed systemic involvement[6] and led to our current use of the term"NSF." Muscle involvement and contracture around joints are especially disabling, confining patients to wheelchairs and making feeding difficult as it did in our patient. Involvement of pericardium, diaphragm, and lung has been described in autopsy studies.[7]



Foci demonstrate thickened deeply eosinophilic collagen within the fat lobules. H&E 40×.



Immunohistochemical stain using antibody targeting CD-34 showing increased numbers positive spindle cells with elongated dendritic processes. CD34 stain 400×.



Thickened collagen in subcutis with clefts and a proliferation of cells with bipolar and oval nuclei. A mildly myxoid stroma (blue hue) is present in foci. H&E 100×.

Pathologic findings have suggested that NSF is an exaggeration of normal wound healing and have emphasized the role of Circulating Fibrocytes (CFs) derived from bone marrow in the fibrotic process. CFs can at least be documented in early lesions by CD34 and Procollagen I staining. Staining of Transforming Growth Factor Beta (TGF-beta), Spindle Cells, Clefts, increased Mucin, and Multinucleated Histiocytes have all been described. The fibrosis extends deep into the fascia layer.[5,8,9]

The differential diagnosis for fibrosing disorders includes Eosinophilic Fasciitis, which was our working diagnosis for this patient, as well Scleroderma, Scleredema, and Scleromyxedema. Evaluations for these diseases require input from Rheumatology as well as Dermatology and Pathology. Full thickness skin biopsy will usually exclude these other processes.[10]

All patients described thus far have had Acute Kidney Injury (AKI) or advanced Chronic Kidney Disease (CKD) stage 4 or 5. Not all have had dialysis support.[11] Liver transplant and Hepatorenal Syndrome have also been associated with NSF.[12] Age, sex and ethnic background have not been factors.[11] High dose Erythropoietic Therapy has been associated with NSF.[12] Risk of NSF has been less than 5% but increases with multiple Gd exposures and higher or double dose (0.2 mmol/kg).

Kidney transplantation or recovery of kidney function have been associated with stabilization or improvement of NSF, but complete recovery has occurred in less than 40% of patients after dialysis was stopped.[14]

Many reported therapies for NSF have not documented subsequent kidney function, which makes it difficult to ascertain the response to that therapy. One treatment that has shown at least early improvement, without any change in GFR, is Extracorporeal Photopheresis (ECP).[15]

At this point, the best treatment for NSF is avoidance of Gadolinium (Gd), especially in CKD stages 4 & 5 (GFR < 30 ml/min/1.73 m^2). Hemodialysis for three

consecutive days can remove almost all of the Gd, but NSF has still occurred despite such treatment.[11] Gd should also be avoided in hepatorenal syndrome and recent liver transplantation.[3,16]

There is no clear consensus about Gd use in CKD stage 3 (GFR <60 ml/min to 30 ml/min/1.73 m^2), but hydration protocols similar to those used with iodinated contrast agents should be employed, and alternatives to Gd should be considered.[4]

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