Nephrogenic Systemic Fibrosis in the Podiatric Patient

Lewis Freed, DPM*
Josh Hill, DPM†
David Gooch, DPM*

Nephrogenic systemic fibrosis (NSF) is a severely debilitating disease that was first described in the literature by Cowper and colleagues in 2000. It is pertinent to the field of podiatry because patients with NSF first manifest cutaneous symptoms in the lower extremity in the form of fibrosing lesions. To date, these lesions have been documented only in people with moderate to severe kidney failure. There is speculation that gadolinium, used as a contrast agent for imaging, might be the inciting factor that triggers a cascade of events that results in the inappropriate fibrosis both in the dermis and in deeper tissues. Nephrogenic systemic fibrosis has been shown to cause these lesions in the lungs, pleura, diaphragm, myocardium, pericardium, and dura mater, the presence of which are typically indicative of severe progression of NSF. In cases where the lesions are manifest in the periarticular tissue, joint contractures and restricted range of motion can often result. We provide a quick synopsis of NSF, and a short case study that describes the authors’ experience with one of their patients who requested a surgical consult as a result of being wheelchair-bound due to NSF’s sequelae. (J Am Podiatr Med Assoc 102(5): 419-421, 2012)

Mendoza et al1 published the first reports of nephrogenic systemic fibrosis (NSF) in 2006. It was originally described as scleromyxedema-like skin lesions in renal-dialysis patients. There has been some dispute over a proper name for the disease because systemic manifestations were not initially documented in the literature. Once this disease was identified, an international registry was produced at Yale University. As of 2008, 200 cases have been reported.2

Epidemiology

Nephrogenic systemic fibrosis is a relatively new fibrosing disorder seen only in patients with moderate to severe kidney failure. It has a strong occurrence with, but is not exclusive to, patients on hemodialysis.3,5 There is no special preference to NSF by gender, race, or age. Neither etiology nor duration of kidney disease have a correlation to NSF.6,7

Pathogenesis

There is no conclusive evidence to prove the cause and mechanism of NSF. Researchers have, however, speculated that there must be an inciting event in patients with advanced renal failure that sets off a cascade of events similar to wound healing,5,8 ultimately resulting in fibrotic lesions in the dermis and at times extending into the subcutaneous tissue. The main culprit under investigation is gadolinium, found in contrast agents, given to patients undergoing magnetic resonance imaging.9,10-13 Evidence of the deposition of gadolinium has been identified in the tissue specimens of some patients with NSF and 95% of patients with NSF have had recent exposure to gadolinium.14

Both theories of how the pathologic tissue fibrosis occurs assume there is an initiating event, such as tissue deposition of gadolinium. The two possible theories include activation of the transforming growth factor (TGF)-beta-1 pathway (2); or an increase in circulating fibrocytes.1,2,15

Clinical Manifestations

Cutaneous symptoms occur in all patients with NSF and some may progress to systemic symptoms.3 Usually there is a latent period between gadolinium exposure and the onset of cutaneous systems. This
latent period has a range of 2 days to 18 months with an average of 2 to 4 weeks\textsuperscript{16,17}

The course of the disease is especially pertinent to the field of podiatry because the first sign of NSF is typically manifested in the lower extremity. Patients typically present with bilateral fibrotic or brawny hyperpigmentation of the skin. Other descriptions include thickened, indurated papules, plaques, or subcutaneous nodules that can be erythematous. These skin lesions start on the ankles, lower legs, feet, and hands and then move proximally. Nephrogenic systemic fibrosis can involve the trunk and buttocks, but the head is spared\textsuperscript{1,18,19}.

It is not uncommon for edema and erythema to precede the lesions. The edema resolves, but the skin retains the thickened, erythematous, and plaque-like texture. It then progresses to become a brawny, furrowed appearance, that is described as “cobblestone,” “woody,” or “peau d’orange.” When this process involves the periarticular tissue, it causes limitations in joint range of motion along with flexion contractures\textsuperscript{1,3-10,20}. It can be so severe that the patient is limited to a wheelchair due to immobility.

Following cutaneous manifestations, systemic involvement such as fibrosis of the lungs, pleura, diaphragm, myocardium, pericardium, or dura mater\textsuperscript{18,21,22} are indicative of severe progression of NSF.

**Differential Diagnosis**

Thick and hard skin or a “peau d’orange” to the extremities can resemble multiple diseases such as systemic sclerosis, scleromyxedema, eosinophilic fasciitis, and calciphylaxis\textsuperscript{1,23,24}, which must be ruled out.

**Prognosis**

The prognosis depends on the extent and rapidity of cutaneous involvement as well as the severity of systemic involvement. Current literature states that 20% of patients with NSF modestly improve, 28% do not improve, and 28% die\textsuperscript{1}. Fulminant NSF is associated with flexion contractures to the degree that the patient loses his or her mobility. This occurs in 5% of patients\textsuperscript{15}. Improvement of the disease has been attributed to improved renal function\textsuperscript{1,7,8,15}; however, this occurred only in a small percentage of the patient population. Currently there is no proven efficacious therapy for NSF.

**Case Report**

A 46-year-old male presented to our East Valley Foot and Ankle Specialists office in Mesa, AZ with a chief complaint of painful contracted bilateral lower extremities and the inability to walk. He had been advised that his legs were unable to be braced and was referred to our office for surgical consultation.

The patient stated that he had been able to walk prior to having a colloid cyst removed from his brain with the use of gadolinium in August 2006. At the time of the procedure, the patient was on peritoneal dialysis.

Approximately 3 weeks after the procedure, the patient started developing symptoms, beginning with a severe rash on his abdomen, chest, and back. The rash was believed to be drug related but continued after cessation of medications. The patient also began experiencing severe pain with arthralgias, joint tightness, and edema. The rash then began to spread bilaterally on his hands and feet and moved proximally toward his elbows and knees. The rash was treated with prednisone and steroid creams, which aggravated the condition.

The patient was referred to the dermatology department at Yale University in October 2006 and given a diagnosis of nephrogenic systemic dermopathy, now known as NSF. The patient was then referred to the specialists at Yale who told him there was no available treatment for him. Shortly thereafter, in an attempt to improve his renal function, the patient was transitioned from peritoneal dialysis to hemodialysis. However, this proved unsuccessful. Doctors then thought a renal transplant would be the patient’s only curative treatment. The patient received a kidney transplant in November of 2007, yet his symptoms have remained and progressed.

Past medical history is significant for hypertension, end stage renal disease, anxiety, hyperkalemia, heart murmur, peritonitis, disc removal, multiple episodes of bronchitis and pneumonia, chronic nausea and vomiting, and plantar verruca.

**Physical Exam**

The patient presented to the office unable to work and using a motorized scooter. He appeared to be awake, alert, and oriented to all spheres and in no acute distress. The patient’s neurological and vascular status appeared to be intact. On dermatologic exam his skin was noted to be hyperpigmented, indurated, contracted, shiny, and paper thin. His musculoskeletal exam revealed rigidly contracted upper extremities. His bilateral lower extremities were in a fixed plantarflexed cavovarus position, with no range of motion available. No pain on palpation was noted. No reflexes or manual muscle testing could be accurately assessed.
Radiographs were consistent with a fixed planterflexed cavovarus deformity, somewhat resembling that of severe cerebral palsy or clubfoot.

The patient presented to our East Valley Foot and Ankle Specialists office in search of surgical treatment because he was advised that bracing was not possible. Being relatively unfamiliar with this particular disease, we advised the patient that we would like to obtain his medical records and consult with local radiology, nephrology, and dermatology experts to determine a proper treatment plan.

Conclusions

Nephrogenic systemic fibrosis is a rare yet severely debilitating disease that we must be aware of as pediatric practitioners. To our knowledge, this is the first report of NSF in the podiatric literature. The purpose of this paper is to increase the awareness of this condition. It is our recommendation that we exercise increased caution with the use of gadolinium imaging in podiatric patients with nephropathy, and keep NSF in our list of differential diagnoses.

References