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Case Report

Nephrogenic Systemic Fibrosis Among Liver Transplant Recipients: A Single Institution Experience and Topic Update

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Nephrogenic systemic fibrosis (NSF) is a recently characterized systemic fibrosing disorder developing in the setting of renal insufficiency. NSF's rapidly progressive nature resulting in disability within weeks of onset makes early diagnosis important. Two reports of NSF after liver transplantation are known of. We present three cases of NSF developing within a few months after liver transplantation and review the current literature. Loss of regulatory control of the circulating fibrocyte, its aberrant recruitment, in a milieu of renal failure and a recent vascular procedure appear important in its development. Known current therapies lack consistent efficacy. Only an improvement in renal function has the greatest likelihood of NSF's resolution. Delayed recognition may pose a significant barrier to functional recovery in the ubiquitously deconditioned liver transplant patient. Early recognition and implementation of aggressive physical therapy appear to have the greatest impact on halting its progression.

Key words: Liver transplantation, magnetic resonance imaging, nephrogenic fibrosing dermopathy, renal insufficiency

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Introduction

Nephrogenic systemic fibrosis (NSF) is a recently characterized systemic fibrosing disorder observed in patients with renal insufficiency. It was initially described as nephrogenic fibrosing dermopathy (NFD) as it was thought to be limited to the dermis, though with increasing recognition its systemic nature has been revealed. Patients may require hemodialysis, peritoneal dialysis or may never require renal replacement therapy.

The pathophysiology of NSF is unknown. Lesions are erythematous, sharply demarcated plaques and nodules, often with a characteristic symmetrical involvement of the legs from midthighs to ankles and midupper arms to the wrist. The trunk may be involved, but the face and back are spared. The involved skin becomes markedly thickened and woody to touch. Pain, causalgia and pruritus are common, and joint contractures may develop quickly, within weeks of onset progressing to joint immobility.

Dermal thickening is a common occurrence in patients with acute and chronic renal failure posing a diagnostic dilemma. The differential diagnoses can include scleromyxedema, scleroderma, calciphylaxis of renal disease, systemic sclerosis and eosinophilic fascitis (1,2). A variety of therapies have been attempted, but no single therapy has been found to yield a consistently positive outcome. The only durable responses have been associated with a return of renal function or renal transplantation.

While over 170 patients have been registered in the NFD registry at Yale University (3) (http://www.icnfdr.org), only a few with end stage liver diseases (ESLD) have been described (2,4), and two reports after liver transplantation are known of (5,6). We present three cases of NSF occurring within a few months after liver transplantation and review the current literature regarding this disorder.

Case Reports

Patient one

A 60-year-old Caucasian male with ESLD secondary to hepatitis B and C, lost his liver allograft to portal vein thrombosis, requiring a retransplantation with a second graft 3 months later. Prior to his first transplant, his baseline creatinine was 1.1 mg/dL corresponding to a glomerular filtration rate (GFR) of 73 mL/min/1.73 m^2. Renal insufficiency progressed over a period of 3 months to end stage renal failure requiring hemodialysis, 1 day prior to his second transplant, with a MELD score now at 40. Dialysis continued for a week in the postoperative period. Three months after retransplantation he presented with a 5-week history of progressive skin tightening and restricted mobility

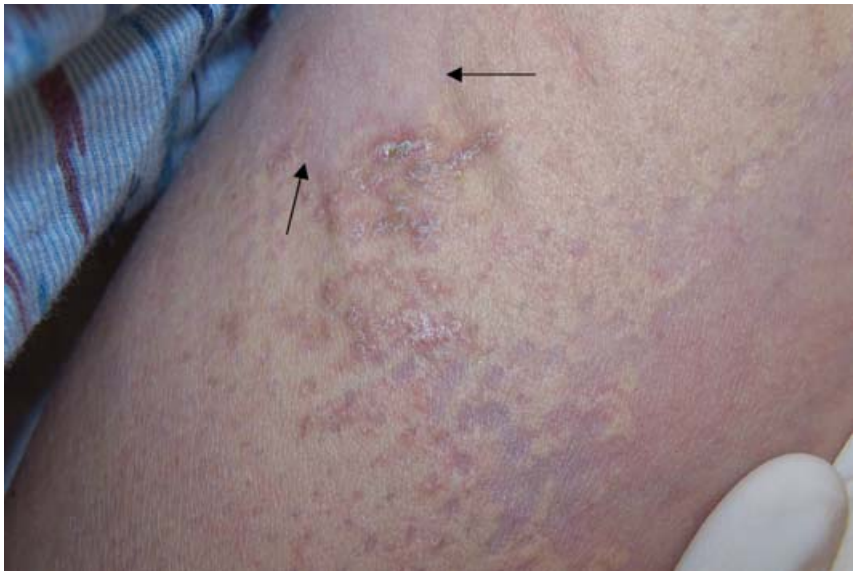

Figure 1: Primary lesions in NSF. This begins as skin colored to erythematous papules, which coalesce into erythematous nodules. The upper part of the figure (arrows) demonstrates the demarcating plaque.

resulting in confinement to a wheelchair. Physical exam revealed firm, diffuse, indurated, painful lesions of both upper and lower extremities from midarm to wrist (Figures 1 and 2) and midthigh to ankles in distribution while his creatinine had increased to 3.2 mg/dL (GFR of 18 mL/min/1.73 m^2). A skin biopsy demonstrated increased number of fibrohistiocytic cells throughout the dermis (Figure 3) with increased mucin deposition and staining positive for CD34 (Figure 4), consistent with a diagnosis of NSF. Two weeks of every other day albumin exchange pheresis was begun while a concomitant decline in his renal function necessitated the resumption of hemodialysis. Gradually, a partial resolution of the skin lesions and symptoms was noted with significant improvement in his mobility to a state where he can now ambulate with the assistance of a walker. His current Cr is 2.8 mg/dL (GFR 25 mL/min/1.73 m^2) and he remains on dialysis.

Patient two

A 51-year-old Caucasian male with ESLD secondary to hepatitis C, hepatorenal syndrome, a MELD of 32 and a preoperative creatinine of 4.0 mg/dL (GFR 17 mL/min/1.73 m^2) underwent liver transplantation. Continuous veno-venous hemodialysis was required on postoperative day three, and continued for 2 weeks until recovery of renal function. Over the next few weeks significant lower extremity edema and pain developed. This progressed to firm, plaque-like lesions on both the upper and lower extremities which were treated unsuccessfully with antibiotics. Bilateral venous duplex studies of the lower extremities demonstrated no evidence of venous thrombosis. At the time of skin biopsy, the patient's serum creatinine was 1.8 mg/dL (GFR 43 mL/min/1.73 m^2), the serum calcium was 10.0 mEq/dL, the serum phosphorus 4.3 mEq/dL and the intact parathyroid hormone level 48.5 (normal range 15–65 pg/mL). After a skin biopsy, the upper extremity lesions were diagnosed as calcinosis cutis, and cinacalcet instituted for serum calcium regulation. Despite adequate control, with serum calcium levels of 7.5–9.5 mEq/dL, these lesions progressed and a concern for calciphylaxis was entertained. Upon a second review, the histopathology of the skin biopsies was felt to be consistent with NSF. Therapy consisted of compression wraps and steroid cream along with the initiation of a rigorous physical therapy program. As his renal function has stabilized, the skin lesions have improved and with intense physical therapy he has regained mobility.

Patient three

A 76-year-old Caucasian male with ESLD secondary to alcoholic cirrhosis and a MELD score of 32, underwent liver transplantation. Acute on chronic renal failure with a baseline creatinine of 2.8 mg/dL (GFR = 24 mL/min/1.73 m^2) necessitated the start of hemodialysis 1 week prior to transplant. Two months posttransplant, during preparation for permanent hemodialysis access, he was noted to have firm woody skin over both forearms and the extensor surface of both thighs. Venous duplex of the lower extremities were unremarkable for venous thrombosis. A punch biopsy of the affected skin was consistent with NSF with fibrohistiocytic invasion of the dermis and positive CD34 staining. At the time of biopsy, his serum calcium was 7.9 mEq/dL, serum phosphorus was 4.1 mEq/dL and intact parathyroid hormone level was 143.5 pg/mL (15–65 pg/mL). The patient refused a recommended course of plasmapheresis; however, he initiated topical calcipotriene ointment and rigorous physical therapy. Over a period of 6 months the patient showed improvement with his contractures, progressing from initially being wheelchair bound, to a stage where he has limited mobility with a cane. He has remained on hemodialysis since transplant.

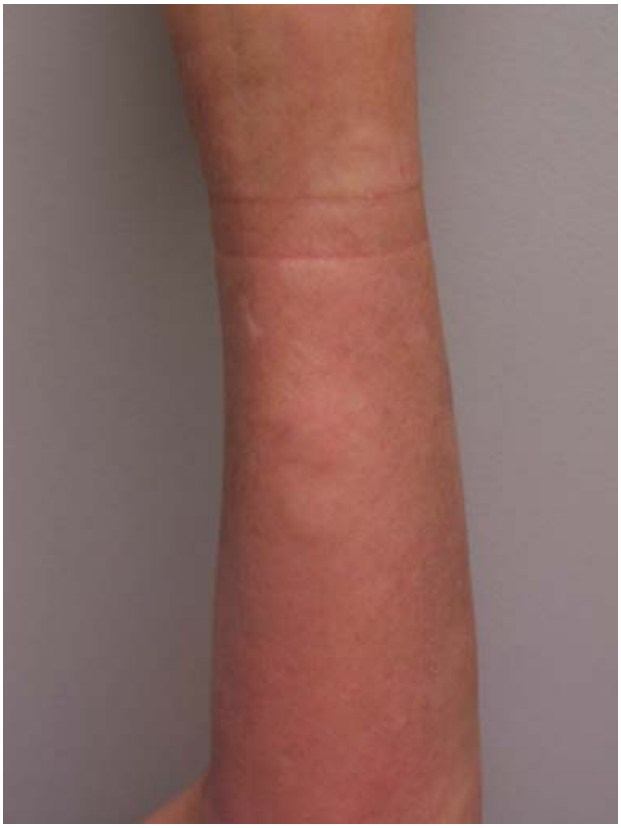

Figure 2: Progression of lesions of NSF. Extensor surface of patient's upper extremity where plaques are seen to be erythematous and coalescing, subsequently resulting in thick fibrotic skin.

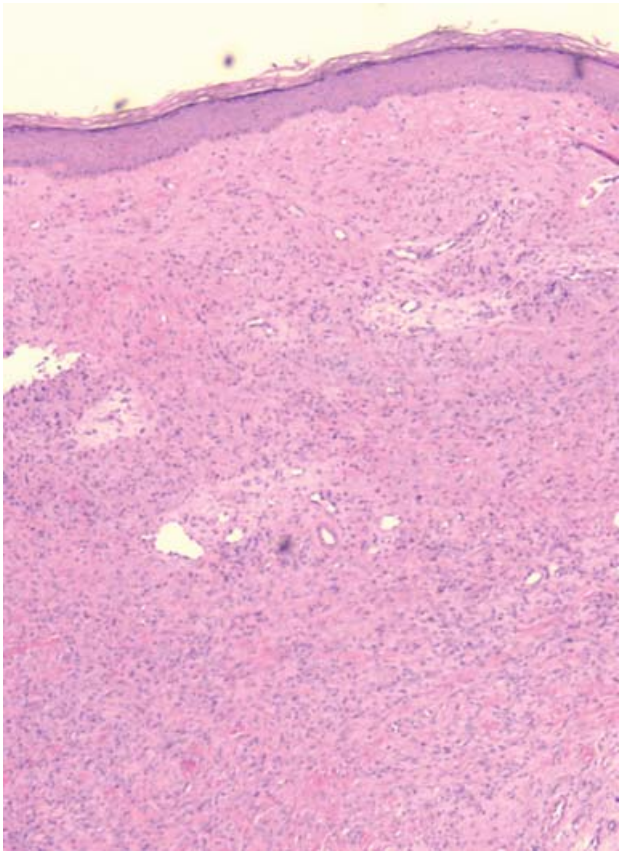

Figure 3: Sections from hematoxylin and eosin stained slides showed a diffuse lesion comprised of fibrohistiocytic cells that filled the reticular dermis.

Discussion

Renal dysfunction is common among patients with ESLD, particularly after liver transplantation. Multiple factors are involved, including acute tubular necrosis and cortical necrosis due to perioperative hypotension, intravenous contrast nephropathy and calcineurin inhibitor nephrotoxicity (7). Although NSF has rarely been described among liver transplant recipients, it is an important consideration in the differential diagnosis of any disorder which results in systemic fibrosis in a patient with renal dysfunction. The extent of NSF's involvement, whether dermis-limited or with extracutaneous manifestations, does not appear to be related to the degree or cause of renal impairment. Conditions which may appear similar to NSF have different treatment modalities making early diagnosis by skin biopsy critical. NSF is progressive and can rapidly lead to contractures and immobility within weeks from the start of symptoms. A deconditioned physical state being ubiquitous among patients after liver transplantation, the disability manifested by NSF may impose a substantial barrier to functional recovery after transplantation.

The original description of NFD appeared in 2000 by Cowper et al. who reported a new scleromyxedema-like skin condition in a series of 14 patients (8). It was not until a year later that the condition was formally characterized as NSF (9). Fibrosis associated with NSF can extend beyond the dermis and since the first report of its systemic involvement in 2003, and multiple reports since (9,10) have led to its current nomenclature as NSF. The fibrotic infiltration of NSF has been described to involve a variety of tissues including subcutaneous, all muscle types, pleura and pericardium, the tunica albuginea, renal tubules, great vessels of the heart extending into the ventricles and septum, as well as facial, pulmonary and cardiac fibrosis (10). Rarely, NSF may progress to dermal calcification (2,9) and even to the extreme of osseous spicules perforating the epidermis (11). A careful histopathological evaluation and the clinically distinct characteristic distribution prevents this variant of NSF to be mistaken for calciphylaxis of renal disease.

The primary lesions in NSF begin as skin-colored to erythematous papules that coalesce into erythematous nodules and sharply demarcated plaques. A characteristic symmetrical involvement of the legs from midthighs to ankles and

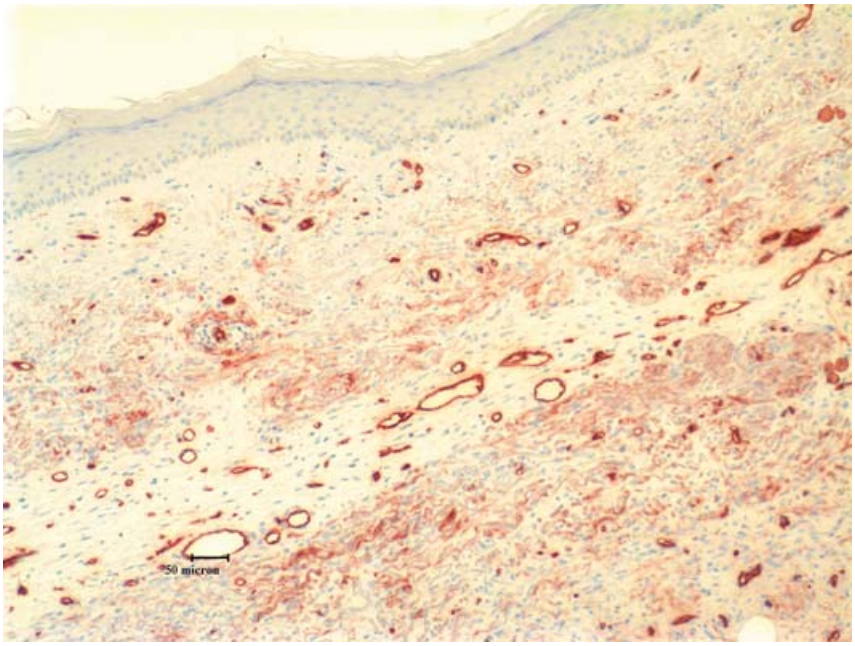

Figure 4: Immunohistochemical stains against CD34 shows focal staining of the spindled cells with CD34.

midupper arms to the wrist with possible truncal involvement is often seen. The lesions are often painful and pruritic. The distribution along the extremities with the lack of facial involvement and the absence of paraproteinemia helps to differentiate it from scleromyxedema with which it is most often confused. Characteristically, patients are noted to have significant anasarca that on gradual resolution reveals the underlying wood-like consistency of the skin in NSF.

Deep biopsy is necessary for accurate diagnosis given the typical nature of the lesions, with subcutaneous and occasionally musculofascial extension. A histopathologic distinction is made from similar fibrosing skin conditions by the increased number of CD34 and procollagen I positive spindle-shaped dermal fibroblasts, accumulation of tissue dendritic cells, thickened collagen bundles with surrounding clefts and large amounts of mucin deposition in the dermis. The microscopic evaluation of the systemic lesions similarly show haphazardly arranged collagen bundles with clefts, composed of dense fibrous tissue with interspersed CD34 positive fibroblast-like cells whether found in pleural, pericardial or muscle tissue.

While no etiologic agent has been found, speculation regarding the recent identification of this condition suggests an association with some newer pharmacological or chemical agent. Recently, Grobner et al. reported on the temporal association between the onset of NSF and the administration of gadolinium-DTPA as contrast for magnetic resonance imaging. Renal insufficiency prolongs the half-life of gadolinium. The authors speculate that the prolonged exposure, or the exposure to an epitope in the correct setting may precipitate NSF (3). Interestingly, all three of our patients had undergone gadolinium based magnetic resonance studies within 2–6 weeks prior to the onset of the symptoms of NSF.

The release of aromatic amines into the blood, such as 4,4′-methylenedianiline with the utilization of resterilized dialysis equipment has also been reported as a source of concern (12). Our institutions' dialysis units do not reuse hemodialysis filters. Also recognized is the fact that increased serum levels of circulating immune complexes and antinuclear antibodies are found in patients with chronic renal failure and hemodialysis. The possibility of abnormal antigenic stimulation and/or sensitization to nuclear antigens resulting in these features observed in patients with immunologically and nonimmunologically driven renal disease is another proposed mechanism of NSF. Given the large number of patients with end stage renal disease and chronic hemodialysis, one would expect to see many more patients with NSF if only one factor was responsible. The Centers for Disease Control and Prevention have investigated NSF (13), concluding that the origin of NSF is most likely multifactorial and the clinical spectrum of hemodialysis-associated fibrosis may be wider than has been suggested.

Cowper et al. introduced the concept that NSF was temporally linked to recent surgical procedures including a vascular component. While 15% of the patients reported a nontransplant related surgical procedure just prior to the onset of NSF, the figure rose to 48% when transplantation was included and finally if hemodialysis access procedures (fistula creation, dialysis catheter placement) were included, the number grew to 90%. This temporal relationship of recent surgery, vascular trauma and NSF onset leads us to

believe that factors related to vascular injury and thus unmasked antigen exposure may play an inciting role (10,14).

Aberrant fibrocyte recruitment is felt to be at the core of its pathogenesis while the cellular composition itself resembles that of a wound healing reaction (2,14). Loss of regulatory control among circulating fibrocytes, the effector cell of NSF, in a milieu of renal failure and a recent vascular procedure are believed to be central to its evolution. The influence of substances such as transforming growth factor β (TGF-β) are known to cause fibroblasts to undergo modulation and it is hypothesized that a persistent signal leads to loss of control of the fibrocyte resulting in their dermal and extradermal deposition along with mucin.

Calcineurin inhibitors and erythropoietin both have known pro-fibrogenic potential through the upregulation of TGF-β and could play a contributory role in the development of NSF. In fact, it has been suggested by Leboit that a dose-reduction of erythropoietin may help to improve NSF in some (15).

The incidence of perioperative renal failure requiring hemodialysis has risen with the use of the MELD criteria. The patients in our series had several of the potential risk factors for NSF, including vascular injury, gadolinium administration and pro-fibrotic medications. At present, it is unclear if the pathophysiology of liver failure and transplantation contribute to this risk. Because anasarca, venous stasis and skin lesions are common in the liver transplant population, the prevalence of NSF may be higher than suspected, warranting a high index of suspicion with early skin biopsy in these situations.

A consistently effective therapy does not exist for NSF as yet. Baron et al. examined three cases of NSF in liver transplant patients receiving plasmapheresis with improvement, though the concurrent improvement in renal function makes it difficult to ascribe the improvement to the treatment or the improvement of the renal function. Similar therapy has met with less or no success in other series (16,17). Another three patients were treated with extracorporeal phototherapy also with varying results from improved mobility to complete lesion resolution (18). Other treatment modalities attempted to treat this condition include corticosteroids, calcipotriene ointment, cyclosporine, cyclophosphamide, thalidomide, isotretinoin, alpha interferon, photodynamic therapy and IVIG (5,17–19). Due to the small number of patients with this condition, meaningful data relating to their treatment efficacy remains lacking.

NSF's course appears to parallel that of the concomitant renal disease. No treatment modality is absolutely effective. Improving renal function either spontaneously or by renal transplant commonly results in improvement of NSF, but is not a guarantee (14,20). Absence of improved renal function has also been reported in some patients who have had a very gradual but spontaneous improvement.

NSF is a recently characterized disorder about which little is known. The collective current thought regarding possible etiologies and pathogenesis may involve multiple inciting events with the circulating fibrocyte playing a central role. Early recognition with aggressive physical therapy appears likely to have the greatest impact on progression of this morbid condition. It is recognized that improvement in renal function correlates with the greatest likelihood of NSF resolution.

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