A moderate response to plasmapheresis in nephrogenic systemic fibrosis

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Abstract

Nephrogenic systemic fibrosis (NSF) is a recently identified idiopathic cutaneous fibrosing disorder that occurs in the setting of renal failure. The disease initially called *nephrogenic fibrosing dermopathy* is closely linked to exposure to gadolinium-based contrast media used during magnetic resonance imaging in patients with renal insufficiency. Although little is known about the pathogenesis of this disease, the increased expression of transforming growth factor-beta has been demonstrated recently. Herein, we present a case of NSF was partially treated due to a moderate and temporary response to plasmapheresis with no recurrence for 6 months, but returned at the end of 6th month.

Introduction

Nephrogenic systemic fibrosis (NSF) is a recently identified idiopathic cutaneous fibrosing disorder that occurs in the setting of renal failure.[1] It is characterized by thickening and hardening of the skin, hyper-pigmented fibrotic papules and plaques typically located on extremities, and disabling flexion contractures. Although the exact pathogenetic mechanisms of NSF have not yet been fully determined, the etiology centers on the use of gadolinium contrast in patients with impaired renal function.[1,2]

Herein, we report a case of NSF that was partially treated with a temporary moderate response with plasmapheresis without any evidence of recurrence for 6 months after the plasmapheresis.

Case Report

A 60-year-old woman presented with the swelling of her arms and legs as well as the stiffness and thickening of her skin with a burning pain for 3 years. She was ongoing hemodialysis for 15 years for chronic kidney disease with an unknown etiology. Coronary magnetic resonance (MR) angiographies were performed twice with a month interval 5 years ago. The lesions appeared one month after the first IV gadolinium enhanced MR angiography. After the onset of severe restricted range of motion of her extremities, she became wheelchair bound in 3 months. Her medical history was notable for hypertension and the hepatitis C virus DNA was positive. Her medications included only hydrochlorothiazide. Dermatological examination revealed diffuse induration of the skin with brown hyper-pigmentation on the distal parts of the extremities. Sclerodactily and bilateral severe flexion contractures of the wrists, knees and ankles were striking (Figure 1). The quantitative measurements of the range of motion (ROM) were also performed. The goniometric measurements of the ROM of her right and left wrist joints were 10 degrees in flexion and extension in order, before the plasmapheresis treatment. The values of the ROM of her metacarpo-phalangeal and metatarso-phalangeal joints were both 5 degrees in flexion and extension in order in both right hand side and left hand side before the plasmapheresis treatment. Her right and left ankle joints had a ROM of 0 degrees in flexion and extension with an accompanying complete flexion contracture before the treatment.

The histopathological examination exhibited thinning of the epidermis, swelling and coarsening of the collagen fibers in the dermis. Atrophy of the skin appendages and fibrosis were also noted together with the medial calcification of the medium-sized arteries (Figure 2). The alcian blue stain showed mucin deposition in the dermis and subcutis (Figure 3). In the immunohistochemical staining of Factor XIIIA and CD 34 antibodies; clefts of Factor XIIIA positive cells in the reticular dermis and CD34-positive dendrocytes intermingled between coarse collagen tracts were seen in order. The scanning electron microscopic examination in cutaneous biopsy specimens taken from the lesional skin demonstrated increase and roughening of the collagen fibers, augmentation of the fibroblasts, concentric thickening of the basal membrane of the blood vessels (Figure 4). But, in higher magnifications of the scanning electron microscopy/energy-dispersive x-ray spectroscopy, the presence of gadolinium wasn't observed.

Laboratory examinations revealed hemoglobin: 8.68 g/dL, hematocrite: 25.5, trombocyte count: 217,000/μL. The peripheral eosinophil count was normal. Blood urea nitrogen: 61 mg/dL, creatine: 4.82 mg/dL. C-reactive protein was 48.5 mg/L and the erythrocyte sedimentation rate was 28 mm/h. Serum calcium was 10.2 mg/dL (normal range: 8.5-10.5 mg/dL) and phosphor was 6.4 mg/dL (normal range: 2.5-4.5 mg/dL). Liver function tests were also normal. The laboratory workup including anti-nuclear, anti-scl 70, anti-centromer, anti-cryoglobulin antibodies, anti-cardiolipin antibodies, lupus anticoagulants and cryoglobulin tests were all negative and excluded autoimmunity. The porphyrin levels of the blood and the feces were normal. The serum protein electrophoresis excluded the presence of the paraproteinemia. Her breath function tests, thorax and abdominal computerized tomography, echocardiography and ophthalmologic examinations demonstrated no evidence of systemic involvement. Her thorax computed tomography (CT) was compatible with past focal bronchiectasies on the anterior segment of her left lung upper lobe.

The characteristic morphology and distribution of the cutaneous involvement, associated with these histological findings, in the context of an underlying renal disease, the patient was diagnosed with NFD, and started on therapeutic plasmapheresis exchange three times a week after the dialysis sessions with her informed consent form taken.

On each plasmapheresis session, 5% albumin solution in 3000 mL Ringer lactate was given in one hour. After the third session, marked regression of the contractures and improvement of the ROM of the extremities were seen. The goniometric measurements of the ROM of her right and left wrist joints were 17 degrees in flexion and extension in order, after the plasmapheresis treatment. The values of the ROM of her metacarpo-phalangeal and metatarso-phalangeal joints were both 10 degrees in flexion and extension in order in

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both right hand side and left hand side after the plasmapheresis treatment. It was also clearly noticed that she was able to move her both ankles after the treatment with a ROM of almost 13 degrees in flexion and 10 degrees in extension in right hand side and 10 degrees in flexion and 8 degrees in extension in left hand side. Skin hardening, edema and the induration of her extremities were also significantly decreased (Figure 5). Normalization of the skin elasticity was highly clear. Improvement was more pronounced on the hands. Although she wasn't able to walk, her limb function was significantly better. She informed that she noticed a significant increase in the range of her motion especially in upper extremities. Plasmapheresis was performed for ten sessions, and withdrawn due to the adverse effects of syncope and hypotension seen just after the plasmapheresis. She also informed that she had taken physiotherapy for her contractures for 2 years without any improvement and had already discontinued physiotherapy 6 months before the treatment of plasmapheresis. No evidence of recurrence was noted on 6 months follow-up. However 6 months after her first presentation the complaints of hardening and stiffness in her extremities restarted partially. As the informed consent wasn't given for the continuing sessions, the plasmapheresis treatment was stopped.

Discussion

For the diagnosis of NSF the characteristic morphology and distribution of the cutaneous involvement, associated with the proper histological findings, accompanying with an underlying renal disease are all required.[3] As this present case had both sclerosing lesions and a history of chronic renal insufficiency, we first had to remind some other possible associated diseases in the differential diagnosis as well. We excluded the diagnosis of localized scleroderma, scleromyxedema, porphyria cutanea tarda, calciphylaxis, eosinophilic fasciitis and eosinophilia-myalgia syndrome. Herein, at the table below the clinical and histopathological differential diagnosis of NFD are summarized (Table 1).[4,5]

Although many treatment modalities such as cyclosporine, thalidomide, interferon, UVA–1, extracorporeal photopheresis, photodynamic therapy and re-PUVA have been used with variable success, there is currently no effective therapy for NSF.[6,7] Plasmapheresis has been reported to be successful in 3 liver transplant recipients with renal dysfunction diagnosed with NSF.[8] They were treated with one to three 5-day courses of therapeutic plasmapheresis exchange at intervals of 2-4 weeks. A moderately or marked clinical improvement in the skin lesions, and amelioration of the joint contractures had also been observed. The patient, who had been treated in the early course of his disease, had the best response to plasmapheresis.[8] Nevertheless, two of these three patients recovered renal function, while they were undergoing plasmapheresis. Therefore, there is a possibility that their lesions could be improved due the recovery of renal function rather than plasmapheresis, since spontaneous remission of the NFS after normalization of the renal function has been well known. Recently, another patient with NSF has been reported who had been treated with 6 sessions of plasmapheresis 3 times a week, and had shown gradual improvement of the skin lesions.[9] Herein at the table below, the comparison of the demographic features of the 5 patients with NSF, the plasmapheresis treatment schedules and the treatment responses in 4 of 5 patients, who showed some improvement with plasmapheresis are summarized (Table 2).[8,9] As we know, three patients who developed NSF after liver transplantation and one of the other two Brazilian cases were all the reported responders to the plasmapheresis treatment in the literature.[8,9] As we see, the time duration from the beginning of the lesions till the onset of the plasmapheresis treatment and the frequency of the plasmapheresis treatment surely positively affects on the treatment results in NSF.

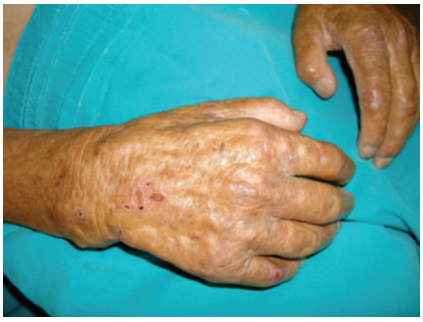

Figure 1. Sclerodactily, and bilateral severe flexion contractures of the wrists.

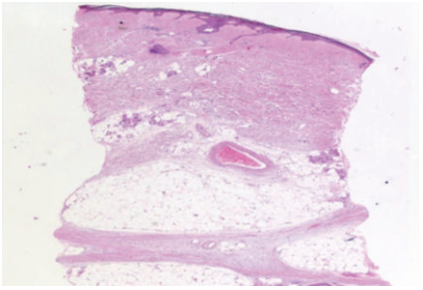

Figure 2. Thinning of the epidermis, swelling and coarsening of the collagen fibers in the dermis with the atrophy of the skin appendages and fibrosis (H&E, X 20).

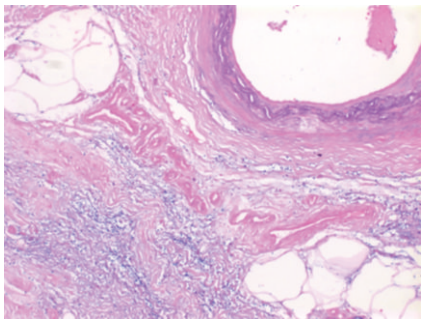

Figure 3. The alcian blue stain showed mucin deposition in the dermis and subcutis.

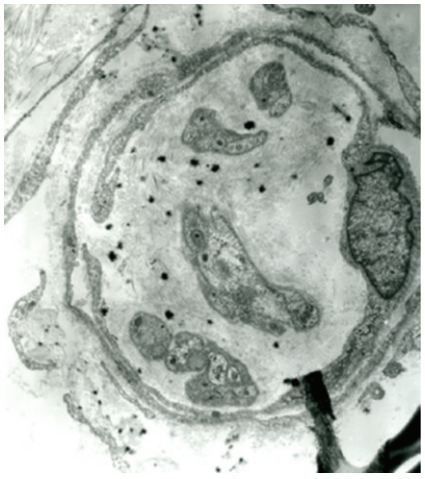

Figure 4. Electron microscopy demonstrated increase and roughening of the collagen fibers, augmentation of the fibroblasts, concentric thickening of the basal membrane of the blood vessels.

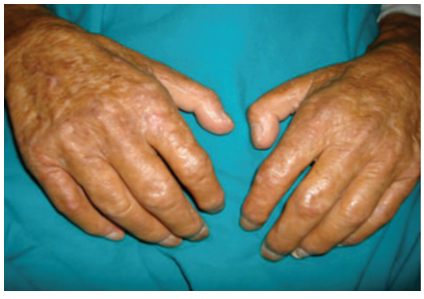

Figure 5. Skin hardening, edema and the induration of her extremities were also significantly decreased.

Table 1. The clinical and histopathological differential diagnosis of nephrogenic fibrosing dermopathy.

	Clinical features	Histopathological findings
Nephrogenic fibrosing dermopathy (NFD)	Thickness of the skin, erythematous or brown colored plaques in peau-d'orange appearance, papules and subcutaneous nodules	Thickening of the collagen fibers, CD 34+ spindle cells, mucin deposition
Localized scleroderma	Ivory colored, sclerotic plaques with livid borders ANA positive or negative and anti-centromer (+)	Thickened, homogenized collagen fibers, mucin deposition, atrophy of the adnexa
Scleromyxedema	Waxy papules on upper extremities, face and neck, sclerodactyly, Ig G paraproteinemia, eosinophilia, myopathy, arthritis, cerebral sympthoms, ocular, renal involvement	Thickened collagen fibers, mucin deposition, fibroblastic infiltration
Porphyria cutanea tarda	Bullae, skin thickening, hypertrichosis, milia and scars in photosensitive areas	Subepidermal bullae, Ig G, C3 deposition at dermoepidermal junction
Calciphylaxis	Echymosis, livedo reticularis, necrosis, escar formation, in the presence of renal insufficiency and high calcium and phosphate	Small sized vasculopathy, mural calcification and thrombosis with intimal proliferation
Eosinophilic fasciitis	Swelling of the extremities, induration and demarcation lines, *Groove*' sign, eosinophilia, high ESR and hypergamaglobulinemia	Hyalinization and thickening of the collagen fibers of the deep fascia and subcutis, eosinophilic collections
Eosinophilia-myalgia syndrome	Diffuse thickening of the skin, trunk and face	Thickening of the collagen fibers, mucin deposition

NFD, nephrogenic fibrosing dermopathy; ANA, anti-nuclear antibody; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin.

Table 2. The comparison of the demographic features of the 5 patients with NSF, the plasmapheresis treatment schedules and the treatment responses in 4 of 5 patients, who showed some improvement with plasmapheresis.

Cases	Age	The duration of the disease	The etiology of the disease	Other systemic diseases	The time from the beginning of the disease to the the plasmapheresis treatment	The schedule of the plasmapheresis treatment	The response to the treatment
The present case	60	One month after the first IV gadolinium enhanced MR angiography.	Unknown etiology	Hypertension and HCV positivity	3 months after the development of the lesions	Three times a week after the dialysis sessions, for ten sessions	Temporary moderate improvement (No recurrence in 6 months follow-up. Later lesions restarted partially)
Liver graft donor case 1.[8]	46	4 weeks after liver TX	Hepatorenal syndrome (hemodialysis After TX for about 1 week)	Cirrhosis, HCV, alcoholic liver disease, hepatocellular carcinoma	3 weeks after the liver transplantation	5 day course of treatment repeated 4 weeks later	Marked improvement even after 24 months later
Liver graft donor case 2.[8]	42	2 months after the development of chronic renal insufficiency	Hypertension and cyclosporine therapy; for 11 years	HCV cirrhosis, alcoholic liver disease	?	5 day course of treatment repeated every 2 to 3 weeks for a total of 3 courses	Mild, 3 months later died due to the multisystem organ failure
Liver graft donor case 3.[8]	50	8 weeks after liver TX	Hepatorenal syndrome (2 weeks after Liver TX)	Gastrointestinal bleeding secondary to HBV, hepatorenal syndrome, g	5 months after liver TX	A single 5-day course	Moderate, was able to ambulate with a cane, 27 months after TX
Brazilian case 1.[9]	23	4 months after renal TX	Polycystic renal disease for 5 years	Renal insufficiency, live-donor renal TX, rejection of the graft	(-) Remission of the lesions after the normalization of the renal function	-	-
Brazilian case 2.[9]	24	Simultaneously with the renal graft rejection	Unknown etiology, for 2 years	Chronic renal disease, live donor renal TX, arterial thrombosis, bilateral iliac vein thrombosis (peritoneal dialysis followed by haemodialysis)	Simultaneously with the beginning of the lesions	6 sessions of plasmapheresis, 3 times a week	Marked improvement, without any recurrence after 1 year follow-up

MR, magnetic resonance; NSF, nephrogenic systemic fibrosis; TX, transplantation; HCV, hepatitis C virus; HBV, hepatitis B virus.

The moderate response seen in our case after 3 sessions of plasmapheresis was noted to be faster and earlier than the other cases treated with plasmapheresis. In Baran *et al.* article, the plasmapheresis treatment in liver graft recipients were mostly performed for 5 sequential days, but less frequently in 3-5 sessions with intervals of 2-4 weeks in longer periods, and the treatment responses were slower than the others at the end of the last sessions.[8] However, in another Brazilian case of Aires et al the plasmapheresis treatment were 3 times a week and the treatment response was also moderate after 6 sessions, similar with our case.[9]

The therapeutic effect of plasmapheresis has been attributed to remove auto-antibodies and other reluctant things from blood, and in dermatology, it has been especially used for the treatment of autoimmune diseases such as pemphigus vulgaris. It has been suggested that plasmapheresis induces a decrease in serum TGF-β levels, which is a pro-fibrotic cytokine. The high levels of TGF-β1 expression suggest that activation of the TGF-β1 pathway may be ultimately responsible for the remarkable tissue fibrosis in NSF. Since TGF-β1 is expressed in dendritic cells and is involved in the regulation of the complex process of dendritic cell maturation, it is possible that the causative agents resulted in increased expression of this growth factor as a part of the response of the dendritic cells to the noxious agent.[10] The TGF-β1 produced by these dendritic cells, in turn, is thought to be responsible for both the fibrotic process and enhancement or initiation of antigen presenting functions of additional dendritic cells, establishing a vicious circle that results in their accumulation in affected tissues. If this possibility is correct, therapeutic approaches aimed at removing TGF-β1 or counteracting its pro-fibrotic effects may be an effective treatment for this currently incurable disease.[10,11] Plasmapheresis is supposed to reduce the levels of plasmatic TGF-β1, thus blocking the pathophysiology of the disease.[9]

Transforming growth factor has previously been found in skin and fascia samples of patients with NSF by in-situ hybridization.[10] The past results suggested the association with TGF-β1 and fibrosis in NSF, with an additional suggestion of Smad involvement as a second messenger. Transforming growth factor β1 is believed to be a central mediator in fibrosis as it induces fibroblasts to synthesize and contract the extracellular matrix. Although TGF-β1 is an important participator in the process of fibrosis, the mechanisms that lead to its production are unclear.[11] Transforming growth factor β1 activators include matrix metalloproteinases (MMP); MMP-2 and MMP-9, thrombospondin-1, plasmin, and integrin avb6. Activated TGF-β1 can then bind to a receptor complex, which will lead to phosphorylation of Smad2/3. These phosphorylated mediators can bind with Smad4 and translocate to the nucleus. Besides, Smad 6 and Smad 7 act as inhibitory proteins to the above mechanism. Transforming growth factor β1 can inhibit its own actions by the induction of Smad7. A recent article suggested that TGF-β1 activation may also occur by transglutaminase 2, which showed increased expression in NSF samples.[12] Other fibrosing conditions have been shown to express an imbalance in matrix metalloproteinase (MMP) expression and their corresponding inhibitors.[12] In a previous immunohistochemistrical study; while the MMP-1 expression was found to be nearly absent in all tested biopsy samples of the 16 NSF cases, MMP-2 and MMP-9 expression was variable but was increased compared to normal skin.[13] Thus targeting some of these cytokines may be important for the discovery of the future treatment options. Transforming growth factor β1 has many complex physiologic roles in humans in addition to its profibrotic properties, including suppression of the immune response and epithelial proliferation.[11] However; caution should be taken in any attempt to block this cytokine. In the literature Denton et al, for example, showed that CAT-192 (Metelimumab); a human IgG4 monoclonal antibody that neutralizes TGF beta 1 had been chosen for further development for the treatment of diffuse cutaneous systemic sclerosis, also known as scleroderma. Besides, it is also reported that it causes some adverse events and mortality when used in patients with early-stage systemic sclerosis.[14] Targeting Smad3 may also be problematic as Smad 3-mutant mice can develop degenerative joint disease and show chronic inflammation and colorectal adenocarcinomas when exposed to TGF-β1.[15] Besides from these possible adverse effects of monoclonal antibodies against to TGF-β1, no mortal adverse effects or risks of plasmapheresis have been reported in the literature up to now.

We think that if we could have the chance to measure the serum level of TGF-β before and after the relapse, it might show a very valuable prognostic marker in NSF. Although, our patient was started treatment 3 years after the onset of her disease, her contractures moderately improved without any aggravation in a 6-month follow-up. We suggest that plasmapheresis may represent a possible therapeutic option for NFS. However, there are not many cases or clinical studies of NSF that have showed plasmapheresis to be superior compared to the other treatments. We believe that the exact effect of this therapy in these responsible cases still remains to be clarified with further investigations. Comparative randomized double blind studies of plasmapheresis and other treatments like UVA-1, extracorporeal photopheresis, photodynamic therapy and re-PUVA should also be performed to examine the first choice and the treatment schedule in NSF.

References

1. Introcaso CE, Hivnor C, Cowper S, Werth VP. Nephrogenic fibrosing dermopathy/ nephrogenic systemic fibrosis: a case series of nine patients and review of the literature. Int J Dermatol 2007;46:447-52.
2. Khurana A, Greene JF Jr, High WA. Quantification of gadolinium in nephrogenic systemic fibrosis: re-examination of a reported cohort with analysis of clinical factors. J Am Acad Dermatol 2008;59:218-24.
3. Afşar RE, Afşar B. [Nephrogenic Systemic Fibrosis: An Update and Literature Review]. Turkiye Klinikleri J Nephrol 2009;4:24-32.
4. Chen AY, Zirwas MJ, Heffernan MP. Nephrogenic systemic fibrosis: a review. J Drugs Dermatol 2010;9:829-34.
5. Mackay-Wiggan JM, Cohen DJ, Hardy MA, et al. Nephrogenic fibrosing dermopathy (scleromyxedema-like illness of renal disease). J Am Acad Dermatol 2003;48:55-60.
6. Tran KT, Prather HB, Cockerell CJ, Jacobe H. UV-A1 therapy for nephrogenic systemic fibrosis. Arch Dermatol 2009;145: 1170-4.
7. Adışen E, Gürer MA. [Extracorporeal Photochemotherapy: Mechanism of Action, Side Effects, Dermatological Indications]. Turkderm 2008;42:39-44.
8. Baron PW, Cantos K, Hillebrand DJ, et al. Nephrogenic fibrosing dermopathy after liver transplantation successfully treated with plasmapheresis. Am J Dermatopathol 2003;25:204-9.
9. Aires NB, Sotto MN, Nico MM. Nephrogenic fibrosing dermopathy: report of two cases. Acta Derm Venereol 2007;87:521-4.
10. Jiménez SA, Artlett CM, Sandorfi N, et al. Dialysis-associated systemic fibrosis (nephrogenic fibrosing dermopathy): study of inflammatory cells and transforming growth factor beta1 expression in affected skin. Arthritis Rheum 2004;50: 2660-6.
11. Kelly B, Petitt M, Sanchez R. Nephrogenic systemic fibrosis is associated with transforming growth factor beta and Smad without evidence of renin-angiotensin system involvement. J Am Acad Dermatol

2008; 58:1025-30.
12. Kelly BC, Markle LS, Vickers JL, et al. The imbalanced expression of matrix metalloproteinases in nephrogenic systemic fibrosis. J Am Acad Dermatol 2010;63:483-9.
13. Parsons AC, Yosipovitch G, Sheehan DJ, et al. Transglutaminases: the missing link in nephrogenic systemic fibrosis. Am J Dermatopathol 2007;29:433-6.
14. Denton CP, Merkel PA, Furst DE, et al. Recombinant human anti-transforming growth factor beta1 antibody therapy in systemic sclerosis: a multicenter, randomized, placebo-controlled phase I/II trial of CAT-192. Arthritis Rheum 2007;56:323-33.
15. Yang X, Letterio JJ, Lechleider RJ, et al. Targeted disruption of SMAD3 results in impaired mucosal immunity and diminished T cell responsiveness to TGF-beta. EMBO J 1999;18:1280-91.