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 that 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-pigmentation of 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 renal insufficiency. Moreover, NSF has been reported in patients with 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. Sclerodactyly and bilateral severe flexion contractures of the wrists, knees and ankles were striking (Figure 1). The quantitative measurements of the range of motion (ROM) 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 metacarlo-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 alcin blue stain showed mucin deposition in the dermis and subcutis (Figure 3). In the immunohistochemical staining of Factor XIIIa and CD 34 antibodies; clefats of Factor XIIIa positive cells in the reticular dermis and CD34-positive dendrocytes intermingled between coarse collagentracts were seen in order. The scanning electron microscopic examination in cutaneous biopsy specimens taken from the extremities 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; thrombocyte 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 paraproteinemnia. 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 metacarlo-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. 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 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 1). 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. 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.
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. |
| **Localized scleroderma** | Thickening of the collagen fibers, CD 34+ spindle cells, mucin deposition. |
| **Scleromyxedema** | Thickened, homogenized collagen fibers, mucin deposition, atrophy of the adnexa. |
| **Porphyria cutanea tarda** | Thickened collagen fibers, mucin deposition, fibroblastic infiltration. |
| **Calciphylaxis** | Small sized vasculopathy, mural calcification and thrombosis with intimal proliferation. |
| **Eosinophilic fascitis** | Hyalinization and thickening of the collagen fibers of the deep fascia and subcutis, eosinophilic collections. |
| **Eosinophilia-myalgia syndrome** | 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 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 | 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 every 2 to 3 weeks for a total of 3 courses | Marked improvement even after 24 months later |
| Liver graft donor case 2 | 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 | 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 | 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 | 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. However, in another Brazilian case of Al the plasmapheresis treatment were 3 times a week and the treatment response was also moderate after 6 sessions, similar with our case.

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. 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.

Plasmapheresis is supposed to reduce the levels of plasmatic TGF-β1, thus blocking the pathophysiology of the disease.

Transforming growth factor has previously been found in skin and fascia samples of patients with NSF by in-situ hybridization. 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 participant in the process of fibrosis, the mechanisms that lead to its production are unclear.

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. Other fibroblastic conditions have been shown to express an imbalance in matrix metalloproteinase (MMP) expression and their corresponding inhibitors. In a previous immunohistochemical 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. 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 pro-fibrotic properties, including suppression of the immune response and epithelial proliferation. 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. 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. 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 contrac-
tures moderately improved without any aggravation in a 6-month follow-up. We sug-
gest 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 thera-
py 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, photo-
dynamic therapy and re-PUVA should also be performed to examine the first choice and the treatment schedule in NSF.

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