

# Nephrogenic Systemic Fibrosis Associated with Gadolinium Use

Chi-Chao Chao,<sup>1</sup> Chih-Chao Yang,<sup>1</sup> Cheng-Hsiang Hsiao,<sup>2</sup> Ming-Kai Pan,<sup>1</sup>  
Chin-Hsuan Lin,<sup>1</sup> Sung-Tsang Hsieh<sup>1,3\*</sup>

Nephrogenic systemic fibrosis (NSF) is an idiopathic, progressive, systemic fibrosis that occurs in patients with renal diseases. Recently, gadolinium-containing contrast (Gd-contrast) has become a suspected causal factor for NFS. This report discusses two female patients with end-stage renal disease, aged 70 and 51 years, respectively, who developed histologically proven NSF after exposure to Gd-contrast. Clinically, both patients were characterized by fibrosis and induration of skin and muscle mainly in the limbs with joint contracture. In the first case, NSF developed gradually after undergoing evaluation by Gd-contrast magnetic resonance imaging (MRI) and subsequent surgery for her urothelial carcinoma. In the second patient, NSF developed after undergoing evaluation by Gd-contrast MRI for her right shoulder bursitis with calcification, and the conditions of NSF continued to worsen after the surgical treatment of this right shoulder lesion. Although the role of Gd-contrast in NSF is still not well known, the correlation in our cases strongly suggests that it should be used with caution in patients with end-stage renal disease. Both of our patients underwent surgery before or during the development of NSF, indicating that the surgical procedure may be a contributing factor. [*J Formos Med Assoc* 2008;107(3):270–274]

**Key Words:** fibroblast, gadolinium, nephrogenic fibrosing dermopathy, nephrogenic systemic fibrosis, renal disease

Nephrogenic systemic fibrosis (NSF) is a newly recognized disease in patients with renal disease.<sup>1</sup> It was initially recognized in dialysis patients with progressive cutaneous fibrosis and was named nephrogenic fibrosing dermopathy.<sup>2</sup> Subsequent reports revealed systemic involvement of other systems such as muscular, diaphragm, pulmonary and cardiac tissues.<sup>3,4</sup> NSF is characterized by fibrosis and hardness of the skin and muscle, with progressive limited motion and joint contraction. The extremities, especially the legs, are the most commonly involved areas, with the trunk being less frequently involved.<sup>5,6</sup> NSF is rare and affects

both genders equally over a wide range of ages (from children to the elderly). Currently, there is no reliable treatment for NSF. The pathogenesis is unknown; both extrinsic and intrinsic factors underlie overproduction of collagens and eventual fibrosis.<sup>7</sup> However, no definite etiology has been established. Recently, gadolinium (Gd)-containing agents used in magnetic resonance imaging (MRI) have become suspected exogenous triggers of NSF.<sup>8</sup> This report discusses two NSF cases that emerged after MRI with Gd-contrast agents. The possible roles of Gd in NSF will also be discussed.

©2008 Elsevier & Formosan Medical Association

Departments of <sup>1</sup>Neurology and <sup>2</sup>Pathology, National Taiwan University Hospital, and <sup>3</sup>Department of Anatomy and Cell Biology, National Taiwan University College of Medicine, Taipei, Taiwan.

**Received:** June 17, 2007

**Revised:** September 2, 2007

**Accepted:** November 6, 2007

**\*Correspondence to:** Dr Sung-Tsang Hsieh, Department of Neurology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.

E-mail: shsieh@ntu.edu.tw



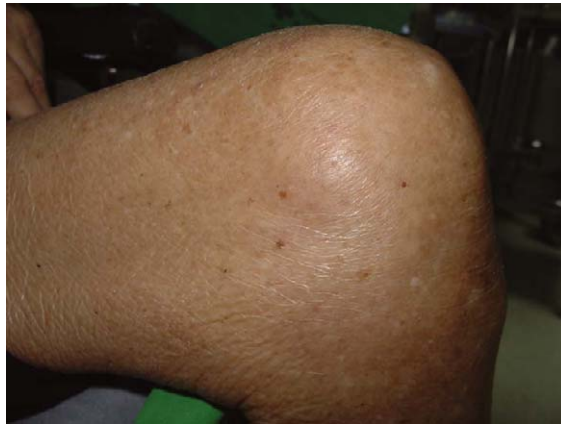
## Case Reports

### Case 1

A 70-year-old female had a history of poliomyelitis with subsequent mild right lower limb weakness. She had chronic renal insufficiency of unknown cause for 8 years and began continuous ambulatory peritoneal dialysis (CAPD) in March 2000. In September 2004, because of a gross painless hematuria, she received cystoscopy and ureteroscopy. Urothelial carcinoma of the bladder, right ureter and right renal pelvis was diagnosed. She underwent transurethral resection of the bladder tumor and laparoscopic retroperitoneal bilateral nephroureterectomy on September 9, 2004 soon after the diagnosis and work-up of the cancer stage was completed.

For cancer evaluation and postoperative follow-up, she received MRI with a Gd-contrast agent (Omniscan, gadolinium diethylenetriamine pentaacetic acid bismethylamide, GdDTPA-BMA; 1464 mg per MRI) four times in September 2004, January 2005, October 2005, and May 2006; there was no tumor recurrence. However, after the operation, a gradual thickening and tightness of the skin and stiffening of the muscles with restricted joint motion in the lower limbs was noted. During this period, she continued to receive regular CAPD and no obvious deterioration in fluid and electrolyte homeostasis was noted.

By late 2005, her knee contractions were so severe that she could not extend her legs and a wheelchair became necessary. She came to the neurologic outpatient department for help in October 2006. Physical examination revealed marked induration and brown hyperpigmentation of the skin of the thigh and leg (Figure 1). Her leg and thigh muscles were stiff and the range of motion in bilateral knees was only around 30 degrees. The trunk and upper limbs were relatively normal. Serum electrophoresis and immune profiles, including antinuclear antibody, rheumatoid factor, anti-Sjögren's syndrome A antigen, anti-Sjögren's syndrome B antigen, anti-Smith antigen, anti-scleroderma antigen (SCL-70), C3 and C4 complement levels, and cryoglobulin levels were all

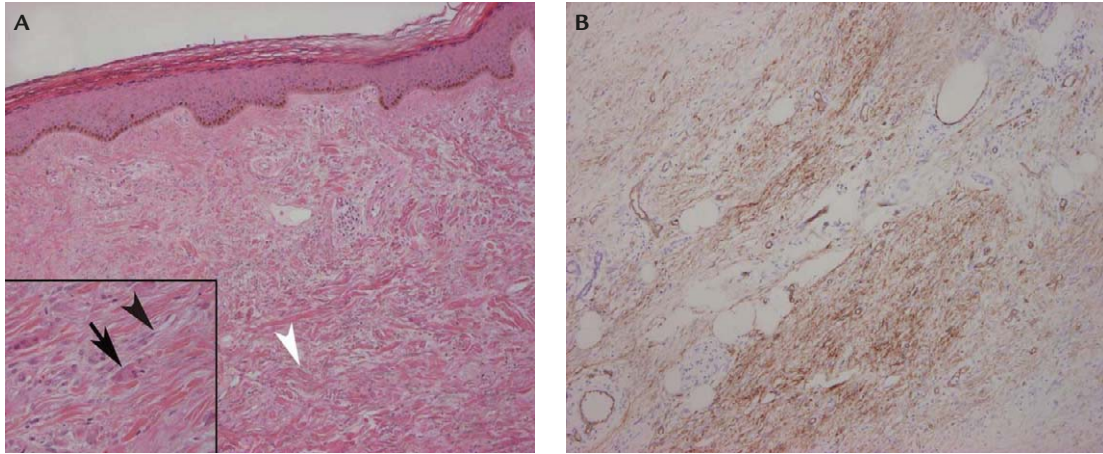


**Figure 1.** Skin changes due to nephrogenic systemic fibrosis in Case 1. The skin of the affected leg is thickened, shiny and hyperpigmented. Joint contraction fixed the knee at the flexion position.

negative. Skin and muscle biopsies from the leg all showed fibrosis and increased numbers of elastic fibers with increased numbers of interstitial epithelioid, stellate and multinucleated cells. Immunohistochemical studies showed some interstitial cells positive for CD34, CD68 and factor XIIIa (Figure 2). She received short-term oral prednisolone but no improvement was noted.

### Case 2

A 51-year-old female had hypertension and chronic renal insufficiency of unknown cause for 11 years. She began to receive CAPD in July 2003. Her condition was stable until February 2006 when she suffered right shoulder pain with a gradually enlarging mass in the same area. She visited the orthopedic outpatient department. MRI with Gd-contrast (Omniscan, GdDTPA-BMA; 1673 mg per MRI) of the right shoulder was performed and showed sub-deltoid bursitis with multilobed calcification. She underwent smooth excision of this mass on April 10, 2006. After MRI, progressive pitting edema in bilateral legs appeared and urine output decreased gradually. There was no obvious deterioration in electrolyte homeostasis, blood urea nitrogen or creatinine. A dialysate with 4.25% dextrose was used to increase ultrafiltration and the edema partially improved. However, skin induration and plaques in the extremities and lower trunk progressively developed. The patient



**Figure 2.** Histology from a skin biopsy of Case 1. (A) Diffuse fibrosis throughout the dermis and subcutaneous fat (white arrowhead, 40×) with increased spindle fibrocytes (black arrowhead, 100×) and multinucleated cells (black arrow, 100×) (hematoxylin & eosin). (B) Immunohistochemical study showed CD34-positive interstitial cells (CD34).

also experienced weakness in all limbs, with progressive limitations in elbow and knee motion. She became unable to walk in May 2006.

She was admitted to the neurology department for suspected myopathy in July 2006. Physical examination revealed hardness and tightness in the skin with limited range of motion in the elbows and knees. Serum electrophoresis and autoimmune profiles, including anti-cyclic citrullinated peptides, antinuclear antibodies, rheumatoid factors, anti-Sjögren's syndrome A antigen, anti-Sjögren's syndrome B antigen, anti-Smith antigen, and anti-scleroderma antigen (SCL-70) were all negative. MRI with Gd-contrast of the extremities was done in July 2006 for suspected soft tissue problems, which revealed nonspecific edematous and inflammatory changes of the limb muscles. However, mechanical respiratory failure of unknown cause with  $\text{CO}_2$  retention ( $\text{PaCO}_2 = 92.8$  mmHg) and loss of consciousness occurred 1 week after MRI. She was intubated and regained consciousness after mechanical ventilation. Skin and muscle biopsies were performed which showed fibrotic changes similar to those observed in Case 1. She received oral prednisolone for 4 weeks and one course of plasma exchange, but no definite responses were noted. Due to no definite etiology being found, CAPD was changed to hemodialysis in August 2006 under the presumption that there might be unknown toxins

that had noxious effects on the muscle and skin and which could not be removed by CAPD.

## Discussion

Our two patients developed NSF after MRI with Gd-contrast. NSF diagnosis in our uremic patients was based on clinical skin and muscle manifestations, and characteristic histologic findings. Diagnoses such as scleromyxedema and scleroderma were excluded through pathologic findings in the skin and muscle and the normal results of serum electrophoresis.

NSF is a recently reported and serious fibrosing disorder that occurs in patients with renal insufficiency of variable duration and severity.<sup>5</sup> Neither dialysis nor transplantation is requisite for its development. There is also no association with any underlying renal etiology or type of dialysis.<sup>7</sup> Clinically, cutaneous symptoms are the most prominent (hyperpigmentation, papules and subcutaneous nodules, skin thickening/hardness). They often lead to a rugged and dimpled texture or *peau d'orange* appearance. The most commonly afflicted areas are the extremities (ankles to thighs and wrists to arms). Truck involvement is less frequent, and the face/neck is rarely affected.<sup>5,9</sup> Afflicted joints usually contract, leading to a restricted range of motion. Patients often become

debilitated as the disease progresses.<sup>6</sup> In some patients, organs such as the heart, lungs, skeletal muscles and diaphragm become involved, which can be fatal.<sup>3</sup>

NSF histology has been documented in previous studies; it has been shown to be distinctive.<sup>2,4,10</sup> Skin biopsies show interconnecting networks abundant with CD34/procollagen dual-positive spindle cells, CD68 and factor XIIIa-positive mono- or multinucleated cells, along with thick collagen and elastic fibers throughout the dermis and muscles. In our patients, similar findings were observed in skin and muscle biopsies.

The mechanism of NSF is not clear. Based on histologic findings, it may be caused by pathologic relocation of circulating fibroblasts (CD34+) to the dermis, muscles and other organs.<sup>7</sup> Additionally, activation and infiltration of CD68+/factor XIIIa+ dendritic cells and increased production of transforming growth factor- $\beta$  may also be involved.<sup>4,11</sup> However, the stimulus for these events is not yet certain. Some studies have proposed trigger factors such as dialysis fluid, drugs such as erythropoietin, cyclosporin<sup>12</sup> or angiotensin converting enzyme inhibitors,<sup>13</sup> and recent vascular surgery.<sup>14</sup> However, epidemiologic studies do not show a consistent picture. Gd-contrast agent administration, before the development of NSF, has recently been noted. Grobner first reported five patients who developed skin abnormalities within 2–4 weeks after Gd-enhanced imaging; the affected patients all had metabolic acidosis.<sup>8</sup> He speculated that in renal failure, combined metabolic acidosis and inadequate Gd-contrast clearance could trigger the development of NSF. Other reports have also noted Gd-contrast exposure before the development of NSF.<sup>14–17</sup> The odds ratio for acquiring the disease after Gd agent exposure has been stated as 32.5.<sup>17</sup> However, the association of metabolic acidosis with NSF is not consistent in these series. The pathologic role of Gd in the development NSF is not yet known and is presumed to involve impaired clearance resulting in deposition of Gd in the skin, muscles or other organs, causing tissue injury and immunologic responses. This hypothesis is

supported by the detection of Gd within the tissues of patients with NSF.<sup>16,18</sup> Due to the link between NSF and exposure to Gd-contrast, the US Food and Drug Administration has issued a warning against the use of Gd-contrast in patients with moderate-to-severe reduction in glomerular filtration rate.

In our two cases, both developed progressive symptoms after Gd-imaging and surgery (for urologic malignancy and right shoulder mass). In addition, Case 2 had acute deterioration including limb edema or weakness of respiratory muscle with CO<sub>2</sub> retention after each administration of Gd-contrast for MRI. These associations strongly suggest a causal relationship between Gd and NSF. Interestingly, our patients both received surgery before or during the development of NSF. This might suggest surgery as a contributing factor for NSF.<sup>14</sup> Some studies indicate that inflammatory events such as major surgery, infection or vascular events play a role in NSF.<sup>19</sup>

In summary, Gd-contrast should only be used with caution in patients with end-stage renal disease, especially in those who have recently undergone or will undergo surgery.

## References

1. Cowper SE. Nephrogenic systemic fibrosis: the nosological and conceptual evolution of nephrogenic fibrosing dermatopathy. *Am J Kidney Dis* 2005;46:763–5.
2. Cowper SE, Su LD, Bhawan J, et al. Nephrogenic fibrosing dermatopathy. *Am J Dermatopathol* 2001;23:383–93.
3. Gibson SE, Farver CF, Prayson RA. Multiorgan involvement in nephrogenic fibrosing dermatopathy: an autopsy case and review of the literature. *Arch Pathol Lab Med* 2006;130:209–12.
4. Daram SR, Cortese CM, Bastani B. Nephrogenic fibrosing dermatopathy/nephrogenic systemic fibrosis: report of a new case with literature review. *Am J Kidney Dis* 2005; 46:754–9.
5. Mendoza FA, Artlett CM, Sandorfi N, et al. Description of 12 cases of nephrogenic fibrosing dermatopathy and review of the literature. *Semin Arthritis Rheum* 2006;35:238–49.
6. Levine JM, Taylor RA, Elman LB, et al. Involvement of skeletal muscle in dialysis-associated systemic fibrosis (nephrogenic fibrosing dermatopathy). *Muscle Nerve* 2004; 30:569–77.

7. Cowper SE. Nephrogenic fibrosing dermopathy: the first 6 years. *Curr Opin Rheumatol* 2003;15:785–90.
8. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006;21:1104–8.
9. Kim RH, Ma L, Hayat SQ, et al. Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis in 2 patients with end-stage renal disease on hemodialysis. *J Clin Rheumatol* 2006;12:134–6.
10. Ortonne N, Lipsker D, Chantrel F, et al. Presence of CD45RO+ CD34+ cells with collagen synthesis activity in nephrogenic fibrosing dermopathy: a new pathogenic hypothesis. *Br J Dermatol* 2004;150:1050–2.
11. Jimenez 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.
12. Swartz RD, Crofford LJ, Phan SH, et al. Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. *Am J Med* 2003;114:563–72.
13. Fazeli A, Lio PA, Liu V. Nephrogenic fibrosing dermopathy: are ACE inhibitors the missing link? *Arch Dermatol* 2004;140:1401.
14. Pryor JG, Poggioli G, Galaria N, et al. Nephrogenic systemic fibrosis: a clinicopathologic study of six cases. *J Am Acad Dermatol* 2007;57:105–11.
15. Lim YL, Lee HY, Low SC, et al. Possible role of gadolinium in nephrogenic systemic fibrosis: report of two cases and review of the literature. *Clin Exp Dermatol* 2007;32:353–8.
16. High WA, Ayers RA, Chandler J, et al. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 2007;56:21–6.
17. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006;17:2359–62.
18. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. *J Am Acad Dermatol* 2007;56:27–30.
19. Sadowski EA, Bennett LK, Chan MR, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007;243:148–57.