No Association between Gadolinium-Based Contrast Agents and Development of Nephrogenic Systemic Fibrosis: a Case Study

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Abstract

Nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, is an emerging systemic fibrosing disorder that develops in the setting of renal insufficiency.

Nephrogenic fibrosing dermopathy (NFD) is a fibrosing condition of the skin which shows an increased number of dendritic cells, fibroblasts and thickened collagen fibers resembling scleromyxedema. It is characterized by indurated plaques mainly on the extremities and the absence of paraproteinemia. Although the exact causes of NSF have not been established, evidence suggests an association between gadolinium-based contrast agents and development of nephrogenic systemic fibrosis. We report a patient who was under dialysis and developed NSF but she never did MRI. *(Iran J Dermatol 2009;12 (Suppl): S19-S22)*

Keywords: nephrogenic systemic fibrosis, nephrogenic fibrosing dermopathy, MRI, Gadolinium

Introduction

Nephrogenic fibrosing dermopathy is an acquired idiopathic disorder which was first reported in 1997[1,3]. Patients with NFD typically develop large areas of hardened skin with fibrotic plaques on their extremities and trunk [2]. Flexion contractures resulting in limited range of motion can also be seen [2,3].

Although the majority of the originally described patients were on hemodialysis for renal failure, more recent reports note that NFD may occur in patients with a history of peritoneal dialysis or renal insufficiency [2].

The diagnosis of NFD is primarily made based on histopathologic features that include proliferation of dermal fibroblasts and dendritic cells, thickened collagen bundles, increased elastic fibers and mucin deposition [2,3].

Nephrogenic systemic fibrosis is a systemic fibrosing disorder that can involve virtually any tissue in the human body and results in significant disability and even death [4]. In the past decade, more than 200 cases of NSF were identified [5].

Gadolinium-based contrast exposure has recently been linked to the development of NSF in patients with underlying kidney diseases and may in fact be the trigger for the fibrosing process [6].

Case Report

A 49-year-old woman presented with diffuse skin thickening that started after the third session of hemodialysis from her trunk and extended to upper and lower extremities. Consequently, she developed painful flexion contractures of her fingers which limited her mobility.

Her medical history was remarkable for a ten-year history of essential hypertension which was controlled by drugs and also bronchectesia.

In 2006, she was developed high blood pressure and increased BUN and Creatinin. During her workup, she never had MRI or CT scan or injection of any contrasts. She received hemodialysis and her skin lesions developed after the third session of hemodialysis with pruritic papules, plaques and subsequently skin thickness (Figure1,2).

Laboratory evaluation, including complete blood count, serum protein electrophoresis, ANA and other studies was unremarkable.

A skin biopsy specimen from an indurated area on her lower leg showed dermis prominently thickened with haphazardly arranged collagen bundles throughout the dermis and subcutaneous septa (Figure 3,4).

It also showed some interstitial edema and irregular spaces separating collagen bundles from each other. In the special staining by Alcian-blue,

mucin depositions were seen in these spaces near the collagen fibers.

She received allograft kidney transplantation in 2008 and within days, the degree of edema and pruritis improved. Her skin, although not completely normal, has become much less indurated and flexion contractures of her fingers have resolved.

Discussion

Nephrogenic fibrosing dermopathy (NFD) is a newly recognized scleroderma-like fibrosing skin condition [7].

It develops in patients with renal insufficiency who are on dialysis therapy or have undergone transplantation [8]. Since its recognition in 1997, several case reports have been published [3].

Although the causative agent remains unidentified, patients characteristically develop areas of thickened skin with indurated symmetric painful papules and plaques affecting the extremities and trunk but the face is spared. Additionally, flexion contractures can develop limiting range of motion [9].

The age of the patients with NFD ranges from 8 to 87 years at the time of onset, with a mean age of 46 years [10]. Some of the clinical manifestations of scleromyxedema are similar to NFD; there are many common features between these two conditions [9].

In contrast to NFD, scleromyxedema typically affects the face and the neck with waxy linearly distributed papules. Skin stiffening with decreased mobility of the mouth is a well described complication of scleromyxedema. Although NFD can result in flexion contractures, patients with scleromyxedema often develop sclerodactyly of the digits as the condition progresses. Patients with scleromyxedema usually have IgG paraprotienemia which can progress to multiple myeloma in about 10% of the patients.

All reported patients with NFD have had normal serum protein levels .The histologic features of NFD also closely resemble scleromyxedema which displays increased collagen and mucin deposition. By contrast, however, inflammatory infiltration with variable numbers of plasma cells, pools of mucin, and fragmented elastic fibers are among the histologic features of scleromyxedema that have not been found in patients with NFD [9].

Histology findings include proliferation of dermal fibroblasts and dendritic cells, thickened collagen bundles, increased elastic fibers, and mucin deposition [9].

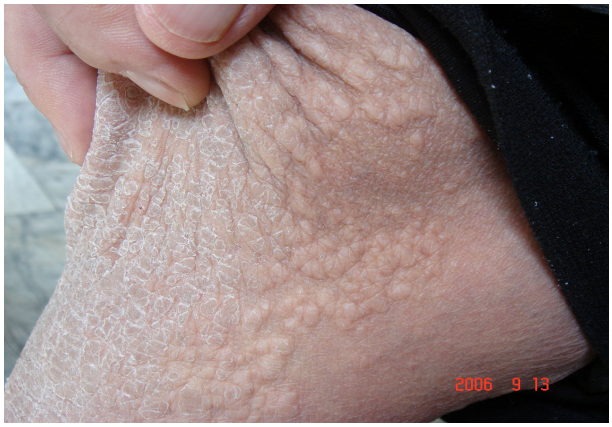

Figure1. *Indurated papules and plaques on the tigh.*

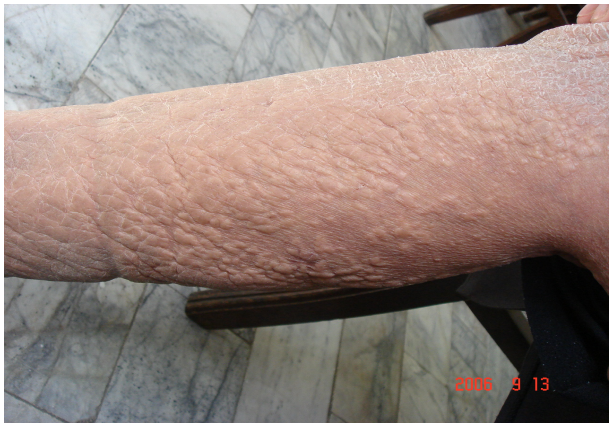

Figure 2. *Indurated papules and plaques on the leg.*

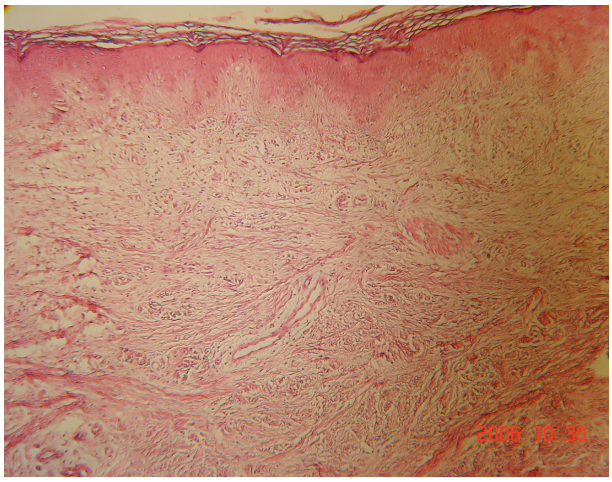

Figure 3. *Histology findings include proliferation of dermal fibroblasts and dendriticdles, increased elastic fibers, and mucin deposition (H&E*10).*

Systemic sclerosis, morphea, porphyria cutanea tarda, eosinophilic fascitis, eosinophilic-myalgia syndrome, and fibroblasic rheumatism should also be considered in the differential diagnosis of NFD [9,3].

Lastly, dual immunohistochemical staining for CD34 and procollagen in the spindle cells of NFD suggests that the dermal cells of NFD may represent circulating fibrocytes recruited to the dermis. In fact, this type of spindle cell proliferation raises the differential diagnosis of dermatofibrosarcoma protuberans or even spindle cell melanoma [9].

Human fibrocytes are mesenchymal progenitors that exhibit mixed morphological and molecular characteristics of hematopoietic stem cells, monocytes and fibroblasts [11].

They likely represent the obligate intermediate stage of differentiation into mature mesenchymal cells of a bone marrow-derived precursor of the monocyte linage under permissive conditions [11].

Studies in various animal models of wound healing or fibrotic diseases have confirmed the ability of fibrocytes to differentiate in to mature mesenchymal cells in-vivo and have suggested a causal link between fibrocyte damage and hypoxia [11].

Many findings indicate that the fibrosis associated with NFD can extend beyond skin and can involve striated muscles, diaphragm, pleura, pericardium, and myocardium, and the fibrosis appears to be due to the effects of a group of cells referred to as fibroblasts. Therefore, it appears that nephrogenic systemic fibrosis would be a more appropriate term for this disease entity [12].

Although the majority of the cases with NSF have been reported in individuals on renal dialysis or those who have received renal transplantation, few cases are reported in patients with acute renal failure without any dialysis [13].

Recent publications suggest an association between exposure to gadolinium-based containing contrast agents used for magnetic resonance imaging and NSF. Among these agents, exposure to gadodiamide is related to NSF more than any other gadolinium-based agent [14].

Preventive measures include use of iodine-based contrast agents, particularly in patients with stage 4 and 5 of chronic kidney disease. If gadolinium contrast is necessary, administration of low volumes of more stable macrocyclic ionic types of gadolinium based-contrast agents is advocated [15].

It seems that not all renally impaired patients who receive gadolinium develop NSF, thus additional risk factors for the development of NSF have been suggested. These risk factors include medications that could cause transmetallation of adolinium, medications that could cause acidosis and high doses of erythropoietin, concomitant medical conditions including hyperphosphatemia, hypercalcemia, iron overload, acidosis, recent surgery, and hepatic diseases. Hypercoagulability and proinflammatory processes may also predispose patients to NSF [6,16].

The most stable gadolinium based- contrast agent is the ionic-macrocyclic chelate GD-DOTA and the least stable agents are the non-ionic linear chelates, gadodiamide and gadoversetamide. GD-CA of low stability are likely to undergo transmetallation and release free Gd ions that may deposit in tissues and attract circulating fibrocytes to initiate the process of fibrosis [17].

However ,the occurrence of NSF after gadolinium contrast agents exposure may vary from negligible up to 2% to 5% in select high risk clinical situations but the prevalence after exposure to two gadodiamide injections is as high as 36% in patients with stage 5 of chronic kidney disease [18].

Broom reviewed 190 biopsy-proven cases of NSF. Of them, 157 cases had MRI with gadodiamide, 8 with gadopentetate, 3 with gadoversetamide and 18 with unspecified Gd-CA. There were 4 confounded cases with more than one Gd-CA. Five cases of NSF were not associated with Gd-CA [4].

Although there are many strong associations between the use of Gd-CA and the occurrence of NSF, our case represents the possibility of other causes for NSF and therefore, we must investigate more for the causes of this condition.

Treatment yields inconsistent results and includes restoration of renal function, extracorporal photopheresis, photodynamic therapy, high–dose intravenous immunoglobulin and other immunosuppressive therapies [10].

Imiatinib, a drug which is used to treat certain types of leukemia, has been reported clinically and histologically effective in a case with severe NSF [19].

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