Treatment of Scleredema Diabeticorum with Tamoxifen

To the Editor:

Scleredema, originally described by Buschke in 1902[1], is a rare scleroderma-tosis of unknown etiology, characterized by nonpitting induration of the skin. In general, scleredema first affects the face and neck, and then may spread symmetrically to the shoulders, trunk, arms, and legs. Cardiac and other organ involvement is rare but restrictive lung disease can be a manifestation.

Three clinical groups of scleredema have been described by Graff[2]. In the first group, the disease starts abruptly after an acute upper respiratory tract infection, often with streptococcal pyogenes and having a tendency to resolve after a period of months to years. The second group begins insidiously without a preceding respiratory tract infection, is of longer duration, and persisting over a period of several years. The third group, known as scleredema diabeticorum (SD), is a chronic form of scleredema associated with severe, often complicated, diabetes mellitus (DM).

SD is characterized by an insidious onset of skin thickening, occurring diffusely over the posterior neck and upper back and occasionally extending to the deltoid and lumbar regions (Figure 1)[3]. It has been reported to occur in 2.5% to 14% of all patients with diabetes. Although numerous treatments have been tried, none have been reported to be effective. We describe 2 cases of SD that showed marked clinical regression following treatment with tamoxifen (tamoxifen citrate).

Case 1. A 61-year-old Chinese woman presented to our Scleroderma Clinic in April 2002 with a 2-year history of progressive skin thickening involving her back, chest, and shoulders but sparing her extremities. There was tightness of her chest with restricted movement of her shoulders, especially with reaching above and behind her head and back. There was no history of Raynaud's phenomenon. She was known to have had insulin-dependent type 2 DM since 1997 with diabetic retinopathy and peripheral neuropathy. Other concurrent diagnoses consisted of hypertension, hypercholesterolemia, obstructive sleep apnea, and primary pulmonary hypertension. Her treatment consisted of Humulin N 35 U before breakfast and 65 U at bedtime, Humalog, triamterene/hydrochlorothiazide, ramipril, furosemide, diltiazem, glimepiride, and continuous positive airway pressure.

Physical examination revealed truncal obesity with a buffalo hump. Her skin was very thick and tight extensively over her back and extending anteriorly over the shoulders to involve the deltoid areas, adjacent chest, breasts, and abdomen. The involved skin was erythematous and warm. The skin over her distal extremities was entirely normal. Her blood pressure was 110/70. The jugular venous pressure was 2–3 cm above the sternal angle; heart sounds were normal with no murmurs. Her chest was clinically clear and abdomen was soft with no tenderness or palpable masses.

Laboratory evaluation showed normal complete blood count (CBC), renal function, liver function tests (LFT), and urinalysis. Fasting blood glucose was 11.5 mM/l and glycosylated hemoglobin was 0.085. Total cholesterol was 5.39 mM/l, triglyceride 1.41 mM/l, high-density lipoprotein 1.53 mM/l, and low-density lipoprotein 3.22 mM/l. Chest computed tomography scan showed no evidence of interstitial lung disease or bronchiectasis. Echocardiography revealed concentric left ventricular hypertrophy and right ventricular systolic pressure of 39–45 mm Hg. Pulmonary function test revealed a mild restrictive defect. Total lung capacity was 3.2 l (81% of predicted), forced vital capacity (FVC) 1.8 l (73% of predicted), forced expiratory volume in 1 second (FEV1) 1.4 l (80% of predicted), FEV1/FVC 81%, and diffusion capacity for carbon monoxide was 70% of predicted.

The appearance and distribution of her skin abnormality was considered to be consistent with cutaneous sclerosis related to her DM. She was treated with methotrexate starting with 10 mg subcutaneously weekly and increasing to 25 mg weekly. After 1 year of treatment with methotrexate, her thickened skin had not improved. D-penicillamine 125 mg daily was added to her treatment regimen but discontinued 7 months later because of a profound loss of taste.

After 3 years of followup, she continued to experience increasing skin tightness on her trunk. Methotrexate was discontinued and she was started on tamoxifen 20 mg twice daily. After 2 months, the skin around her trunk was softer and shoulder movements were improving. After 4 years of treatment with tamoxifen, the diffuse skin tightness on her back had softened remarkably and her shoulder movements were almost normal with only mild restriction. The dose of tamoxifen was reduced to 20 mg once daily. After about 1 year on the lower dose she reported a gradual increase in skin tightness and was put back onto tamoxifen 20 mg twice daily.

Case 2. A 54-year-old Filipino woman attended our Scleroderma Clinic in 2008 with a 5-year history of skin thickening, initially over the back of her neck but progressing over a period of 2 years to involve the upper back and palms of her hands. She was known to have hypothyroidism and an 18-year history of type 2 DM but no Raynaud's phenomenon. Treatment consisted of insulin aspart and insulin glargine, synthyroid, acetylsalicylic acid, rosuvastatin, oxycodone, and diclofenac/misoprostol. She was initially treated by a dermatologist in 2003 with a combination of hydroquinone, tretinoin, and desonide cream, with no improvement.

Physical examination was normal except for an extensive area of skin hardening and thickening involving the neck and the upper trunk posteriorly. Movements of both shoulders were limited; she could only raise her

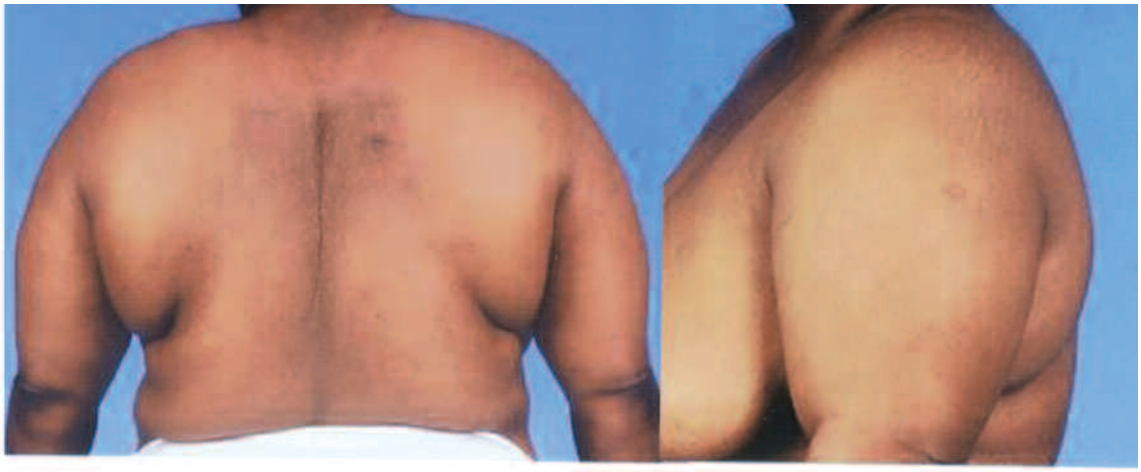

Figure 1. Skin thickening and hyperpigmentation on the back and extending forward to involve the shoulders and chest in a patient with scleredema diabeticorum not treated with tamoxifen.

arms to the shoulder level. The skin over the palm of both hands was also thickened with severe flexor tenosynovitis involving multiple fingers with limited flexion and triggering. Laboratory results showed normal CBC, renal function, and LFT. A diagnosis of SD was made.

The tenosynovitis was treated with multiple corticosteroid injections, with marked improvement and resolution. She was started on tamoxifen 20 mg twice daily. Reassessment 4 months later revealed softening of the skin on her back. The dose of tamoxifen was reduced to 20 mg once daily after 8 months because of vaginal discharge. Evaluation by a gynecologist with an endometrial biopsy was negative. Her last assessment in our clinic after 18 months of treatment with tamoxifen revealed considerable softening of the skin on her back and resolution of the palmar scleredema; she was now able to fully raise both arms to above her head. Tamoxifen was discontinued in January 2010 because of persistent vaginal bleeding and within 2 months she noticed increased tightness of the skin on her upper back and palms.

Scleredema is frequently mistaken for systemic sclerosis (SSc), although the distribution and pattern of skin involvement in these 2 distinct clinical entities are quite different[4]. The hands and feet are usually spared, in contrast to SSc. Furthermore, Raynaud's phenomenon, telangiectasia, and nailfold capillary abnormalities are not seen in scleredema.

The pathogenesis of SD is thought to be similar to other forms of fibrotic complications seen in DM such as nerve entrapment syndromes and tissue contractures. There is evidence suggesting widespread derangements in collagen metabolism in insulin-dependent DM; the collagen appears to be more insoluble, resistant to enzymatic degradation, and associated with increased cross-linking[5]. Further, advanced glycosylation endproducts may directly stimulate the local production of connective tissue growth factor, which in turn enhances the accumulation of connective tissue molecules[6]. These abnormalities were found to correlate with increased DM duration, glycemic control, and longterm complications.

No effective treatment is known for SD. A number of therapies, including corticosteroids, cyclosporine[7], methotrexate[8], penicillamine, UVA1 phototherapy[9], psoralen with ultraviolet light A administered systemically, topically or through bath therapy[10], electron beam, and glycemic control with prostaglandin E_1[11], have all been tried, with limited success.

Tamoxifen is a selective estrogen receptor modulator with a known antifibrotic effect. It appears to be effective in retroperitoneal fibrosis. In 1991, Clark, *et al* were the first to use tamoxifen in the treatment of retroperitoneal fibrosis[12]. Its mechanism of action is not entirely clear, and different hypotheses have been proposed. Tamoxifen may alter the balance of growth factors in such a way that fibroblast proliferation is inhibited[13]. Further, the antiangiogenic properties of tamoxifen may also contribute to its efficacy[14]. Tamoxifen treatment has been demonstrated to decrease the function of fibroblasts derived from Dupuytren's affected fascia and downregulate transforming growth factor beta–2 production in these fibroblasts. However, in a limited study it was found not to be effective in patients with SSc[15].

In our patients, treatment with tamoxifen was effective, with significant improvement of skin thickening and joint mobility. This effect was apparent within months of starting treatment.

Apart from SD, Case 2 also had thickening of the skin and fascia of her hands, with flexion contractures and extensive tenosynovitis. This condition in patients with DM is commonly known as diabetic cheiropathy and has been reported to occur in up to 53% of patients with diabetes, mostly in those with type 1 disease[16,17]. As with SD, its occurrence has been correlated with both quality of blood sugar control and the development of retinopathy. The cheiropathy seen in our patient also improved following treatment with tamoxifen.

We believe that the mechanism of action is likely similar to that in cases of retroperitoneal fibrosis treated with this medication. These data suggest that further studies of tamoxifen in the treatment of localized sclerosing disorders are warranted.

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J Rheumatol 2010;37:12; doi:10.3899/jrheum.100561