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ORIGINAL ARTICLE

The impact of depression, microvasculopathy, and fibrosis on development of erectile dysfunction in men with systemic sclerosis

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Abstract This article is a small case series that aims to discuss the impact of depression, vascular, and fibrotic changes on development of erectile dysfunction (ED) in patients with systemic sclerosis (SSc). In this paper, we present five male patients with SSc, aged 30–48 years. All patients are nonsmokers, and their past medical history does not reveal any other diseases or treatment procedures (drugs) that may have influence on erectile function. We used a five-item questionnaire, the International Index of Erectile Function (IIEF-5), to assess ED in our patients. Microvascular abnormalities (estimated by nailfold capillaroscopy), fibrotic changes (assessed by skin score, chest X-ray and reduction in forced vital capacity), and presence of depression (estimated using the Beck's Depression Inventory) were evaluated. To assess efficacy of sildenafil citrate (25–50 mg 1 h before each sexual activity), patients with ED filled up the IIEF-5 before and after 1-month therapy. We concluded that ED is a frequent and early clinical feature in men with SSc. Microvascular abnormalities are similar in patients with and without ED. Although patients with ED had higher depression indices, an unsatisfactory response to sildenafil citrate indicates that psychoneurogenic factors are not crucial in development of ED in SSc. Patients with ED had more extended fibrotic changes, which indirectly suggests that fibrosis of the corporal body may play the main role in the pathogenesis of ED in SSc.

Keywords Impotence · Systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a clinically heterogeneous generalized disorder that affects the connective tissue of the skin and internal organs such as gastrointestinal tract, lungs, heart, and kidneys. It is characterized by alterations of the microvasculature, disturbances of the immune system, and by massive deposition of collagen.

Erectile dysfunction (ED) is a common, but often underestimated, clinical feature in men with SSc. The prevalence of ED in SSc has been reported as ranging from 12 to 81% in different studies [1–3]. The pathogenesis is not clearly defined. Most of the literature support that ED associated with SSc is due to underlying vasculopathic and fibrotic changes. Raynaud's phenomenon is often associated with ED, despite maintenance of libido [1]. The penile blood pressure was found to be lower in SSc patients with ED than in patients without ED and controls with rheumatoid arthritis [4]. Pathological findings suggest penile arterial alterations and collagenization of the corporal body [5]. Microvasculopathy and tissue fibrosis are potential organic causes, but psychogenic, neurogenic, and comorbid factors may play an important role as well.

This small case series aims to assess the impact of depression, vascular, and fibrotic changes on development of ED in men with SSc.

Case 1

A 39-year-old man presenting with a history of diffuse SSc reported presence of ED. The disease started 10 months ago, at first with Raynaud's phenomenon, and 2 months later, with skin fibrosis spreading very quickly over the entire body. At the same period of disease course, he noticed first difficulties to get and keep an erection during sexual intercourse. The patient was treated with intravenous cyclophosphamide monthly in a dose of 500 mg/m^2 body surface for last 6 months, cisapride (5 mg three times per day), and ranitidine (150 mg/day). His past medical history did not reveal any other diseases that may have influence on erectile function. Physical examination results demonstrated sclerodermatous skin changes extended on face, neck, hands, forearms, upper arms, legs, thighs, and the trunk as well. The value of the modified Rodnan Skin Score was 34. Peyronie's disease as result of penile skin fibrosis was diagnosed by a urologist. Enlarged capillaries, as well as small-to-medium-sized areas with loss of capillaries, were found on nailfold capillaroscopy. Esophageal hypomotility was noticed by contrast esophagography. The radiograph of the lungs showed interstitial lung fibrosis, whereas lung function tests demonstrated restrictive dysfunction (forced vital capacity [FVC]=73.5%). No signs of heart or renal involvement were found. Erectile function was assessed using a validated and standardized self-assessment questionnaire, the International Index of Erectile Function (IIEF-5). The questionnaire consists of five questions (see Table 1). The value of the IIEF-5 index was 11, indicating presence of severe ED. Using the Beck's Depression Inventory (BDI) [6], we did not find symptoms of depression (see Table 2). After 1-month therapy with sildenafil citrate, the value of IIEF-5 index increased from 11 to 16, but the erectile function was still not satisfactory.

Table 2 Beck's Depression Inventory (BDI): interpretation of results

Total score level	Interpretation
0–9	These ups and downs are considered normal
10–18	Mild-to-moderate depression
19–29	Moderate-to-severe depression
30–63	Severe depression

BDI is a fully validated self-administered 21-item questionnaire. The highest score on each of the 21 questions is 3; the highest possible score for the whole test is 63. The lowest possible score for the whole test is zero.

Case 2

A 30-year-old man presenting with a 58-month history of diffuse SSc noticed ED about 10 months after beginning of Raynaud's phenomenon. The patient was treated at first with D-penicillamine (600 mg/day) for 8 months, later with methotrexate (7.5 mg weekly) without significant success. Two years ago, intravenous cyclophosphamide "pulse" therapy was started, concomitantly with low dose of methylprednisolone (6 mg/day), propafenone (300 mg/day), and nifedipine (10 mg three times per day). His past medical history did not reveal any other diseases. Examination of the skin demonstrated diffuse sclerodermatous changes (m-Rodnan skin score=31). Decreased capillary density, enlarged capillaries, as well as small-to-medium-sized areas with loss of capillaries were found on nailfold capillaroscopy. Severe visceral organ involvement was noticed: esophageal hypomotility, interstitial lung fibrosis, restrictive lung dysfunction (FVC=75.1%), and supraventricular extrasystolic arrhythmia. Creatinine clearance was within normal limits; no urine abnormalities were found. The value of the IIEF-5 index was 17. The BDI index was 14, indicating presence of mild-to-moderate depression. The patient did not

Table 1 Structure and contents of the International Index of Erectile Function (IIEF-5) questionnaire

Questions	Answers				
How do you rate your confidence that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
When you had an erection with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always
During sexual intercourse, how difficult was it to maintain your erection to the completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never	Much less than half the time	About half the time	Much more than half the time	Almost always or always

The answers are assessed on a 1–5 scale. The IIEF-5 index represents the sum of all scores. The lowest possible index value calculated using this questionnaire is 5 and the highest 25. If the calculated value is 21 or less, the patient can be considered as having ED.

take sildenafil citrate because he had no sexual activities during the study period.

Case 3

A 34-year-old man presenting with a 10-month history of diffuse SSc noticed ED simultaneously with beginning of first disease symptoms. The patient has been treated with monthly intravenous cyclophosphamide "pulse" therapy (500 mg/m^2 body surface), low dose of prednisone (10 mg/day), diclofenac (100 mg/day), propafenone (300 mg/day), and omeprasole (20 mg/day). His skin score was 25. Decreased capillary density, enlarged capillaries, as well as small-to-medium-sized areas with loss of capillaries were found on nailfold capillaroscopy. Esophageal hypomotility was present, but without lung fibrosis or serious restrictive lung disease (FVC=79.6%). The patient had supraventricular extrasystolic arrhythmia. The value of the IIEF-5 index was 7. The BDI index was 16, indicating presence of mild-to-moderate depression. After 1-month therapy with sildenafil citrate, the value of IIEF-5 index increased from 7 to 11, but the erectile function was still not satisfactory.

Case 4

A 48-year-old man presenting with a 15-year history of limited SSc did not report ED at examination (IIEF-5 index= 21). From the disease onset until present day, the patient did not take immunosuppressive drugs. He was treated just symptomatically: ranitidine (150 mg/day), methoclopramide (10 mg twice daily), and pentoxifiline (400 mg twice daily). Sclerodermatous skin changes were noticed only on fingers and face (m-Rodnan skin score=6). Esophageal hypomotility was found. Enlarged capillaries, as well as small-to-medium-sized areas with loss of capillaries, were observed on capillaroscopy. No signs of lung, heart, or renal involvement were noticed. Using the BDI, we did not find symptoms of depression.

Case 5

A 40-year-old man presenting with a 5-year history of diffuse SSc did not report ED (IIEF-5 index=23). During the first 2 years, the patient was treated just symptomatically, but the last 3 years, he is taking methotrexate (10 mg weekly), omeprasole (20 mg/day), and captoprile (25 mg twice per day). Examination of the skin demonstrated sclerodermatous changes on hands, feet, forearms, and face (m-Rodnan skin score=18). Decreased capillary density, enlarged capillaries, as well as small-to-medium-sized areas with loss of capillaries were found on nailfold capillaroscopy. Esophageal hypomotility was present, but interstitial lung fibrosis on chest X-ray or restrictive lung dysfunction was not noticed (FVC=94.2%). Heart or renal damage was not found. The BDI index was 6 (no symptoms of depression).

Discussion

ED occurs very frequently among men with SSc. Several vascular, fibrotic, or psychoneurogenic factors have been suggested in the pathogenesis of ED in SSc, but the pathophysiologic mechanisms have not been clearly defined. We assessed the potential influence of microvascular abnormalities, fibrotic changes, and depression on development of ED in five young male patients with SSc. All patients were younger than 55 years, nonsmokers, and had no other diseases that may have influence on erectile function (like arteriosclerosis, diabetes, alcoholism etc.). None of patients were treated with drugs that may cause erectile problems. In all patients, erectile function was assessed using a validated and standardized self-assessment questionnaire, IIEF-5.

Three patients with ED ("Cases 1, 2, and 3") reported that their impotence occurred very early in the disease (average 4 months after first disease symptom). Other authors found that ED occurs 2.7±1.2 years after diagnosis [3]. Early development of ED suggests that micovasculopathy may be the main reason for erectile problems. But no significant difference in microvascular abnormalities on nailfold capillaroscopy has been observed between patients with and without ED in this study. However, there are many studies that strongly support the vasculogenic basis of ED in SSc. Nowlin et al. [4] found that four of six impotent SSc patients in their study met the criteria for the diagnosis of "vasculogenic ED" (penile blood pressure index <0.6) [7]. Evidence for vascular abnormalities and penile arterial insufficiency also comes from pathological researches [5, 8, 9].

In comparison to patients with normal erectile function ("Cases 3 and 4"), patients with ED ("Cases 1, 2, and 3") had higher skin scores, more frequently lung fibrosis on chest X-rays and restrictive lung disease, as result of severe interstitial fibrosis. Considering everything, we suppose that fibrosis of the corporal body is more common and more severe in patients with ED. Development of Peyronie's disease, a condition characterized by fibrosis of the corporal body and penile skin, in one patient with ED in our group supports this speculation. Indeed, severe collagenization of the corporal body was found in pathological studies in patients with SSc and ED [5, 8, 9]. Hong et al. [3] reported that SSc subjects were more likely to have a changed

appearance of the penis, suggesting that ED was due to fibrosis of the penile skin and/or corporal body. Simeon et al. [2] discussed a possible causal association between SSc and Peyornie's disease. Thus, our results and most of the literature support that ED in patients with SSc is due to underlying vasculopathic and fibrotic alterations.

However, many psychosocial and comorbid factors can also contribute to development of ED in men with SSc. Mood disorders are expected because pain and functional impairment are common during the course of SSc, and the skin change is disfiguring. Two studies conducted in the USA [10, 11] reported depression in 48–50% of outpatients with SSc. A cross-sectional study in France [12] showed very high prevalence of depression (48%) and anxiety (64%). Using the BDI, which is a widely exploited and validated self-evaluation questionnaire, we found symptoms of depression in two of the three patients with ED, and in none of two patients with normal erectile function. After 1-month therapy with sildenafil citrate, the erectile function was still not satisfactory. Although patients with ED had higher depression indices, an unsatisfactory response to sildenafil citrate indicates that psychoneurogenic factors are important, but not crucial in development of ED.

This paper showed that ED is a frequent and early clinical feature in men with SSc. Patients with erectile problems have more extended fibrotic changes, which indirectly suggests that fibrosis of the corporal body may play the main role in the pathogenesis of ED in SSc. Development of Peyronie's disease in one patient with ED strongly supports this hypothesis. Obviously, patients with limited SSc have a lesser chance of developing ED than patients with diffuse cutaneous disease.

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