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CLINICAL CASE REPORT: ASSOCIATION BETWEEN TYPE 2 DIABETES AND SCLERODERMA SYNDROME

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Introduction. Sclerodema syndrome is a connective tissue disorder of possibly autoimmune etiology, characterized by thickening, hardening, and painlessness of the skin. In some cases erythema and pigmentation of the skin and systemic are present. Some studies have highlighted the association between scleroderma and poor metabolic control in patients with diabetes. *Case report.* A 72-year-old woman with type 2 diabetes mellitus on insulin therapy was admitted to the clinic for metabolic re-evaluation. On examination, the patient had cutaneous erythema, skin hardening and induration. A skin biopsy established the diagnosis of scleroderma. The patient has diabetes for 19 years with poor metabolic control. *Discussion.* The clinical cases of scleroderma in patients diagnosed with diabetes mellitus include subjects with: poor glycemic control, long duration of affection and treatment with insulin. *Conclusions.* The clinical case presented all of factors involved by the specialty literature in scleroderma associated with diabetes. The patient followed treatment with local topical and hydroxychloroquine. According to the latest dermatological consultation, the evolution of skin manifestations was stationary.

Key words: scleroderma, type 2 diabetes mellitus, poor glycemic control.

INTRODUCTION

Sclerodema syndrome (morphea) is a connective tissue disorder of possibly autoimmune aetiology, characterized by thickening, hardening, and painlessness of the skin. In some cases erythema and pigmentation of the skin and systemic determinations (the most common being kidneys, lungs, heart, esophagus) are present.

Three types of scleroderma have been described. Type 1 scleroderma affects patients younger than 20 years. Bacterial and viral infectious have been implicated in this subtype. Type 2 sclerodema is associated with paraproteinemias, respectively the presence of monoclonal gammopathy of the Immunoglobulin G kappa type. Type 3 sclerodema is more observed in patients with diabetes mellitus and poor glycemic control[1].

Numerous studies have highlighted the association between scleroderma and poor metabolic control in patients with diabetes[2–5]. The pathogenesis of scleroderma associated with diabetes is not completely elucidated. Martin C and colleagues mention the following possible mechanisms involved in the occurrence of scleroderma in diabetic patients: "*It has been proposed that nonenzymatic glycosylation of collagen fibers may alter its degradation. Other hypothesis suggests that glucose may stimulate fibroblast proliferation and the synthesis of extracellular matrix components. Immunological response has also been postulated, as some patients have ameliorated following treatment with cyclosporine, but the lack of lymphocytic infiltrates in the dermal lesions seems to rule out a T-cell-mediated etiologic mechanism*"[4].

Case report. A 72-year-old woman with type 2 diabetes mellitus on insulin therapy was admitted to the clinic for metabolic re-evaluation. The patient

was diagnosed with type 2 diabetes in 1999 and followed up with oral antidiabetic therapy until the year 2006. Due to low glycemic control under the conditions of the dietary regimen in 2006, insulin therapy was initiated. The patient also presented associated diseases: postmenopausal osteoporosis, hypertension, dyslipidemia, autoimmune thyroiditis. When examining the patient the presence of cutaneous erythema in the sub-mammary area and skin and induration have been highlighted. The patient was directed to a dermatology clinic where a skin biopsy was performed which established the diagnosis of scleroderma. Histopathological examination performed in 2012 revealed focal epidermal atrophy, dermo-hipodermic fibrosis with thick collagen strips that include focal glomeruli of sweat glands. During the admission in the dermatology clinic, the patient had a normal blood count and moderate inflammatory syndrome in the absence of a detectable infection. Immunological investigations have highlighted the presence of anti SCL-70 (anti-topoisomerase) and anti-Ro antibodies and the absence of centromere antibodies. During the hospitalization, an ophthalmic examination was performed which confirmed the Sicca syndrome. No pathological changes were observed in the musculoskeletal ultrasound examination, Doppler venous exam of lower limbs or the capillaroscopic examination.

The patient had diabetes for 19 years with poor metabolic control. The fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) are presented in Table 1.

Table 1

Characteristics of metabolic control during the evolution of the disease

Years	HbA1c (%)	FPG (md/dl)
2008	9.11	188
2009	10.02	223
2010	9.01	197
2012	6.71	211
2013	9.40	171
2014	8.51	203
2015	10.40	214
2016	9.73	243

The patient is in treatment with bolus basal insulin from 2013. Considering multiple comorbidities, corticotherapy was not recommended. The patient followed treatment with local topical and hydroxychloroquine. According to the latest dermatological consultation, the evolution of skin manifestations was stationary. The presence of cutaneous erythema in the sub-mammary area and skin and induration in patient with diabetes mellitus type 2 in treatment with bolus basal insulin are presented in Figure 1.

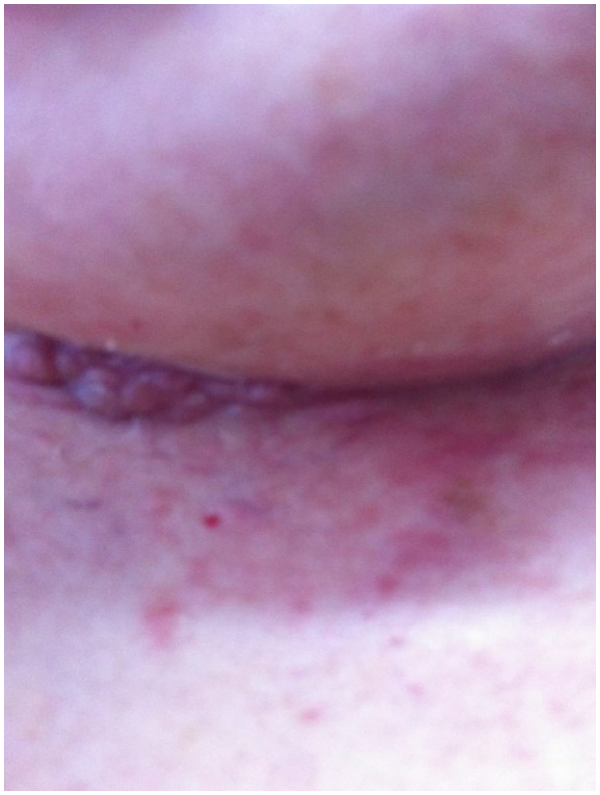

Figure 1. Cutaneous erythema in the sub-mammary area and skin and induration in patient with diabetes mellitus.

DISCUSSION

According to literature data scleroderma occurs in approximately 2.5–3% of patients with diabetes[6]. Satter MA and co-authors reported a prevalence of scleroderma of 14% in 100 hospital diabetc patients[7].

The sclerodema in diabetic patients include subjects with the following characteristics: poor glucose management, long duration of affection, insulin therapy and microangiopathic complications[4]. The clinical case presented all the factors involved in scleroderma.

A review of 33 cases of sclerodema, published in 1984 by Venencie PY *et al.* mentions that diabetic patients were on insulin therapy and had poor glycemic control. Increased glycemic values may result in the activation of fibroblasts to produce abundant matrix proteins in the skin[8]. The proliferation of fibroblasts is associated with

inflammatory infiltrate. In 2013 Glibane AJ and co-workers mention that "*Fibrosis, like wound healing, is instigated by fibroblast activation, proliferation and migration of these cells into the site of trauma and deposition of matrix proteins such as fibronectin and collagen. Fibroblasts are highly active cells and each cell synthesises approximately 3.5 million pro-collagen molecules per day*"[9]. According to some studies the frequency of scleroderma appears to be associated with the duration of diabetes and increasing with age[1, 10]. The patient was diagnosed with a microvascular complication respectively distal sensory polyneuropathy. In a review published in 1998 by Haustein UF and Anderegg U in the Journal of the European Academy of Dermatology and Venerology it is mentioned that "*the microvascular system is one of the first targets involved (damage of capillaries, enhanced expression of adhesion molecules interacting with lymphocytes, perivascular infiltrates as starting points for tissue fibrosis). The immune system is unbalanced (selection of T-cell subpopulations, elevated serum levels of several cytokines, occurrence of autoantigens to topoisomerase I, centromeric proteins and RNA polymerases)*"[11].

Improvement of low glycemic control usually does not improve the sclerodema and diabetes contraindicates some of the therapies reported in the specialty literature[12].

Scleroderma occasionally coexists with other autoimmune diseases such as autoimmune thyroiditis. In a review of 245 patients with scleroderma Leitenberger JJ and co-authors assert that "*18% of subjects had a concomitant rheumatic or other autoimmune disorder, an occurrence four fold higher than that in the general population including all races and socioeconomic strata. But when analyzed by subtype, generalized morphea had a statistically significant association with autoimmune disease with 49% of generalized morphea subjects affected representing 12 times the risk of the general population*"[13]. It should be noted that the patient was diagnosed with autoimmune thyroiditis with elevated ATPO (autoantibodies against thyroid peroxidase) values but with normal TSH (thyroid-stimulating hormone) and FT4 (free thyroxine).

Conclusions. The clinical case presented all the factors involved by the specialty literature, in scleroderma respectively: poor glucose management, long duration of affection, and microangiopathic complications. The patient followed treatment with local topical and hydroxychloroquine. According to the latest dermatological consultation, the evolution of skin manifestations was stationary. The data from the literature does not confirm the improvement of scleroderma after improving glycemic control.

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