

# Coexistence of scleroderma-like syndrome and idiopathic myelofibrosis in a 54-year-old female patient

## Case report

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**Abstract:** Systemic sclerosis (SSc) is characterized by immunological disturbances, vascular damage and overproduction of extracellular matrix by stimulated fibroblasts. It has been postulated that immunological reactions involved in the pathogenesis of SSc may promote the development of malignancies. Coexistence of this disease with neoplastic processes is relatively frequent. In our report we describe a case of a 54-year-old woman with scleroderma-like syndrome, which has preceded the occurrence of idiopathic myelofibrosis by many years. Owing to multiple repeated diagnostic tests we managed to diagnose this disease at the early stage, which enabled effective therapy with remission of blood dyscrasia as well as inhibition of skin lesions and lung fibrosis.

**Key words:** idiopathic myelofibrosis, scleroderma-like syndrome, systemic sclerosis

## INTRODUCTION

Systemic sclerosis (SSc) is characterized by immunological disorders, vascular damage and activated fibroblasts extracellular matrix overproduction. It is related to complex interactions between endothelial cells, lymphocytes and macrophages, taking place through various mediators; cytokines, chemokines, and growth factors released by inflammatory and mesenchymal cells which play an important role in the fibrosis process. It is suggested that immunological reactions involved in the SSc pathogenesis may promote cancer development. Some cytokines involved in the SSc pathogenesis with the profibrotic effect, like transforming growth factor  $\beta$  (TGF $\beta$ ), are present in large amounts in the neoplasm (i.e. breast, ovary, or kidney) [1]. The incidence of cancer in scleroderma is estimated at 3–7% [2], in some studies even at 11.4% [3], and it is 2.1 times higher than in the general population (standardized incidence ratio – SIR), and in the case of lung cancer even 16.5 times greater. The relative risk for hematologic malignancies

was found to be 2.3 times higher than in the general population [4].

The most frequent scleroderma related types of malignant neoplasm are: lung cancer, breast cancer, neoplasms of the hematopoietic and lymphatic systems. An advanced age at the time of the SSc diagnosis markedly increases the risk of cancer [5]. It is believed that immunosuppressive drugs used in SSc (i.e. cyclophosphamide) may induce cancer. [6] On the other hand, drugs used in cancer therapy, like docetaxel [7], paclitaxel [8], bleomycin [9] and others, may induce scleroderma-like syndromes, related most probably to a local excessive accumulation of subcutaneous metabolites. The coexistence of chronic myelomonocytic leukemia, Waldenström disease, Burkitt lymphoma, immunocytic lymphoma and acute and chronic myelogenous leukemia, have been reported [10].

Spontaneous bone marrow fibrosis is a myeloproliferative syndrome, during which the stem hematopoietic cell clone proliferation, excessive interleukin 8 synthesis and an increased number of defective megakaryocytes, which can produce TGF $\beta$ , are observed.

In our article we describe a case of a 54-year-old woman with a scleroderma-like syndrome, which preceded spontaneous myelofibrosis occurrence by several years.

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## CASE REPORT

A 54-year-old patient was for the first time admitted to the Rheumatologic Department in 1995. She complained of painful and edematous ankles, forearm and lower leg skin hardening, and Raynaud's sign. On physical examination a discrete face erythema, forearm and lower leg skin hardening, forearm rash papular alterations, ankles and knees edema, single crepitations at the lung base, the enlarged liver of homogeneous density and elevated blood pressure values were found. Laboratory tests showed normocytic anemia and leukocytosis 15,600/ $\mu$ l with a normal peripheral blood smear. Acute-phase protein levels were normal, as was the erythrocyte sedimentation rate. A slightly enhanced interstitium could be found on the chest X-ray, therefore, functional tests, the high resolution computed tomography (Fig.) and the lung bronchoscopy with bronchoalveolar lavage were performed. The examinations showed interstitial lung disease with lymphocytic alveolitis. To elucidate a cause of hepatomegaly, testes were performed and showed features suggesting autoimmune hepatitis (liver sonography and computed tomography, elevated alanine and aspartate aminotransferase and alkaline phosphatase activity, smooth muscle cells antibodies at a 1:40 titer). Viral and bacterial hepatitis was excluded (viral hepatitis type B and C antibodies and Virus Surface Antigen – HbsAg negative tests results, as well as cytomegalovirus infection, infectious mononucleosis and leptospirosis negative tests results). At the same time antinuclear antibodies (ANA) tests revealed a nonspecific picture: patchy luminescence type ANA at a titer 1:320, negative anticentromere antibodies (ACA) and anti-topoisomerase 1 (anti-Scl-70). The skeletal system radiograph and the densitometry showed the presence of generalized osteoporosis (the value of femoral neck peak bone mass was 3.13 standard deviations). The diagnoses "*Alveolitis. Hepatitis autoimmunologica. Dermatitis. Osteoporosis*" were established. They took into account the complex syndrome affecting several organs without the identification of a specific connective tissue disease.

During five consecutive years the patient was admitted to the hospital several times in the Department of Rheumatic Diseases. Because of persistent leukocytosis (18,000–19,000/ $\mu$ l) cancer diagnostics was performed (chest and abdominal computed tomography, gastrointestinal tract endoscopy, tests for laboratory cancer markers). Bone marrow aspiration biopsy was carried out several times. The function of circulatory and respiratory systems were particularly carefully monitored. The possibility of a coexisting infection was considered. In view of increasing pulmonary arterial hypertension, progressing pulmonary fibrosis, and the rise of hepatic injury indicators, corticosteroid therapy (at a dose of  $\leq 10$  mg with the periodic therapy with pulses of Solumedrol) and immunosuppression (azathioprine 1  $\times$  100 mg) were started.

In September 2000 the patient was hospitalized for hepatomegaly, which was accompanied by splenomegaly. On physical examination, exacerbation of skin lesions and the presence of numerous teleangiectasies on the skin of cheeks and the face were observed additionally. Laboratory findings showed an alkaline phosphatase level rise, leukocytosis (16,000/ $\mu$ l) with a



**Fig.** High resolution computed tomography. Linear and micronodular densities in lower fields of both lungs, with features of interstitial lung disease in the patient

normal peripheral blood smear, elevated D-dimer and fibrinogen levels. Antiphospholipid antibodies were not found. On the abdominal ultrasound, thrombosis of the portal vein was detected. Anticoagulants were initiated.

In April 2001, in an ambulatory blood smear blast cells were observed. Rising leucocytosis (17,000–19,000/ $\mu$ l), the presence of all development stages of granulocytes in the blood smear, anemia with teardrop-shaped erythrocytes, single schistocytes, elevated alkaline phosphatase, the prolonged activated partial thromboplastin time and the D-dimer level rise were found in the laboratory tests. The bone marrow biopsy revealed erythrocyte maturation arrest at the stage of erythroblast, and the mieloblasts and promyelocytes percentage at the upper normal values level. The trepanobiopsy with a diminished number of bone marrow cells, megakaryoblasts and megakaryocytes clusters, an accompanying irregular interstitium proliferation and the presence of collagen fibers, as well as the trabecular bone sclerotisation, finally confirmed the suspicion of bone spontaneous myelofibrosis. The patient was treated with appropriate doses of azotiprine, hydroxycarbamide and prednisone.

In December 2004 the patient suffered from a severe cerebral stroke. The computed tomography of the head showed a subarachnoidal hemorrhage. The patient was unconscious for many weeks; high arterial blood pressure persisted with normal renal parameters and the normal kidney Doppler images. Angiotensin-converting enzyme inhibitors were administered in increased doses. Cytostatic agents and therapy aimed at improving the cerebral blood circulation were continued.

At present the central nervous system abnormalities prevail in the clinical presentation including a slight paresis of upper extremities, tactile sensation disorders, symptoms of delusional and the psychoorganic syndrome. Repeated magnetic resonance examination revealed traits of chronic cortex and subcortical ischemic lesions. Currently we do not observe

hematological disease exacerbation; the hematological and hepatic parameters are within normal value ranges. We do not observe the worsening of skin lesions or progression of lung alterations. The patient is being surveyed by specialists in rheumatology, hematology, psychology and neurology.

## DISCUSSION

Scleroderma and scleroderma-like syndromes may be induced by a number of factors: triptofan, crystalline silica dust, aromatic hydrocarbons, solvents, aliphatic chlorinated hydrocarbons, vinyl chloride, trichloroethylene, epoxid resins, carbidope, pentazocine, coca-ine, fenfluramine or D-penicylamine. Some substances, for example organic solvents, may be common risk factors for the occurrence of malignancies and SSc. Silicon implants play a special role; a greater relative risk of SSc occurrence has been demonstrated in the population of females who underwent breast silicon implant grafting [11,12]. No exposition to any of the above mentioned chemical or physical factors was demonstrated in the patient described in this paper; the patient, a farmer by trade, had no contact with these agents during her life.

In the described case internal organs affections typical of SSc, i.e. lungs affection with an interstitial disease and pulmonary hypertension development, and the central nervous system affection were observed. No alterations in the gastrointestinal tract were found. Other organ manifestations had a nonspecific to SSc course (arterial hypertension, venous thrombosis, hepatomegaly). At the same time, from the very beginning of the disease no scleroderma specific antinuclear antibodies were found. The above symptoms justified a careful approach regarding the disease diagnosis and required a continuously repeated differential diagnosis.

Higuchi et al. [13] found that a statistically significant neoplasm development risk factor in SSc was the presence of ACA, while the erythrocyte sedimentation rate, lactic dehydrogenase,  $\gamma$ -globuline level, ANA or the presence of anti-SCI-70 were not related to the risk of cancer. Hence the assumption that a patient with ACA should be monitored for the presence of neoplastic process. On the other hand, Derka's reports did not demonstrate any differences in antibody profile in patients with SSc, with or without cancer [14]. It seems however that the above mentioned tests should rather be seen as additional diagnostic tools due to highly differentiated dynamism of alterations and various clinical and laboratory presentation of SSc.

In the pathogenesis of malignant alterations in systemic sclerosis patients it has been suggested that anti-Scl-70 antibodies (present in 10–15% of SSc patients) directed against related to the repair of DNA topoisomerase 1, may alter the repair of DNA damages and in consequence induce carcinogenesis. On the other hand, ACA (present in 80% of limited systemic sclerosis patients) may be associated with chromosome damage and malignant transformations. Similarly, E-selectin, which expression is enhanced in SSc [15] through its ef-

fect on endothelial cells, may promote tumor invasion through angiogenesis activation; what is more, cancer cells may show ligand expression towards E-selectin and adhere to endothelial cells, thus facilitating metastase formation. Through this mechanism systemic sclerosis may lead to favorable conditions for neoplasm dissemination.

Alterations of scleroderma-like type (scleroderma-like) being a paraneoplastic syndrome may in turn be related to factors released by the cancer. An enhanced expression of the connective tissue growth factor and type I collagen has been demonstrated; while it has not been found for the TGF $\beta$ .

The SSc patient's genome may be damaged, there may be a greater frequency of chromosome ruptures, deletions and centric fragments and an increased number of accidental repeats. The genome is more fragile than in healthy individuals and additionally damaged by immunosuppressive drugs, which can promote carcinogenesis.

Some cytokines with the profibrotic effect, related to SSc pathogenesis (as TGF $\beta$ ), occur in high levels in some neoplasms (breast, ovary, kidney) [1]. The chance that these immunologic alterations may be the reason for an increased occurrence of malignancies compared to SSc is controversial [16].

In the described case the clinical symptoms of the scleroderma-like syndrome preceded the symptoms of spontaneous myelofibrosis by some 8 years. During this period leucocytosis with the absence of typical myelogram cells in the peripheral blood smear and in myelogram was observed. Trepanobiopsy along with other characteristic symptoms (splenomegaly, neutrophilpoietic line cells, the presence of erythroblasts and teardrop shaped cells) enabled the diagnosis; no cytogenetic tests were performed. A hematological disease effective therapy led to skin lesion cessation and pulmonary fibrosis development.

In many cases a clear differentiation between SSc and the paraneoplastic symptom is necessary. The traits speaking in favor of the paraneoplastic process are: neoplastic history, also in the family, exposition to carcinogens, disease occurrence at an advanced age (more than 45 years of age), general symptoms (fever, fatigue, weight loss), a close time relationship between the appearance of paraneoplastic symptoms and cancer discovery, a weak response to conventional treatment, a symptomatic improvement after oncologic treatment and repeated symptoms occurrence with the cancer recurrence. Scleroderma-like skin lesions particularly often coexist with gastric, breast, and lung cancer, melanoma and myeloma. It is advised to cautiously observe all clinical and laboratory symptoms and verify the diagnosis of the systemic connective tissue disease from the point of view of neoplastic process.

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