CASE REPORT

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Rapidly progressive course of systemic sclerosis sine scleroderma: a case report and short literature review

ABSTRACT

Systemic sclerosis (SSc) is an autoimmune disease that affects the connective tissue. It is progressive and characterized by a diverse course, resulting in a heterogeneous clinical picture. One form of SSc is systemic sclerosis sine scleroderma which affects only 10% of patients. Common manifestations such as skin involvement, Raynaud's phenomenon or telangiectasia are not always the first signs of the disease, which is particularly important for the proper establishment of a diagnosis and initiation of treatment. The success of therapy depends on the stage of the disease, but even with appropriate ongoing treatment, it may not yield the desired effects.

A rare case of systemic sclerosis with delayed cutaneous manifestation was reported. The disease appeared as acute renal insufficiency. Skin involvement was clinically overt and detectable after development of kidney failure. Earlier the patient had enhanced titer of anti-topoisomerase I (Scl-70) antibodies and unspecific alterations visible at capillaroscopy only. The patient required treatment with dialysis, intravenous cyclophosphamide was initiated, followed by oral administration, with good tolerance and achieving reduction of symptoms. Nevertheless, the disease was very severe, rapidly progressive, and fatal.

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KEY WORDS: systemic sclerosis with delayed skin manifestations; scleroderma renal crisis; severe course of systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a systemic connective tissue disease of unknown etiology and unclear pathogenesis. Diffuse cutaneous and internal organ fibrosis in patients are suggested to be resulted from vascular and immune disfunction. There is a variety of clinical courses of the disease and it remains unclear if SSc is a single specific nosological entity or a group of diseases with different etiopathogenesis and similar clinical features. Most of the patients suffer from either diffuse systemic sclerosis or limited systemic sclerosis [1–3]. Only a small percentage of patients suffer from systemic sclerosis without cutaneous involvement (systemic sclerosis sine scleroderma, ssSSc) or overlap syndromes of SSc and another systemic connective tissue disease, most commonly polymyositis [4]. Early SSc was identified in the last decades as a condition characterized by Raynaud's phenomenon, puffy fingers, disease-specific autoantibodies, and microvascular alterations detectable at capillaroscopy, and the condition associated with a very high risk for development of a full clinical picture of SSc [5, 6].

The diagnosis of SSc can be difficult, and skin involvement commonly facilitated the diagnosis. Cutaneous manifestations are usually the first signs of SSc recognized by the patients and cause the patient to see a doctor. When cutaneous symptoms and signs are absent or appeared in an advanced stage of clinically overt disease, diagnosis of ssSSc is difficult and delayed in most of the patients

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[4]. That is the reason of ambiguity in determination of real incidence of ssSSc. This form of the disease is rare but also underdiagnosed. It is an important clinical challenge because early diagnosis of any form of SSc is associated with administration of organ-specific management. Such therapy can increase a quality of life of the patients and enhance their survival prognosis. "Hidden" course of ssSSc resulted in misdiagnosis of a group of patients and they are considered as those suffering from other disorders leading to internal organ disfunction [7]. We report a case of a rapidly progressive ssSSc that appeared clinically as renal insufficiency of unknown cause.

CASE PRESENTATION

A fifty-six-year-old female patient was first admitted to the internal medicine ward of the municipal hospital due to edema of the upper and lower limbs and feeling of "cold" hands. She was discharged from the hospital with diagnosis of undifferentiated connective tissue disease. The main abnormality detected was relatively high titer of antinuclear antibodies, i.e., 149 IU/ml (normal value < 23 IU/ml). No other abnormalities were detected in performed laboratory tests. Methylprednisolone in a dose of 6 mg/day was administered and continued after discharge from the hospital.

Six months later, she was admitted to the Department of Internal Medicine, Rheumatology and Clinical Immunology of the Medical University of Silesia in Katowice due to "pitting" edema of the legs and forearms without induration of the skin. Additionally, edema of the eyelids and anisocoria (higher in the right eye) was revealed. Consulting neurologists suggested computed tomography (CT) scan of the head with administration of the contrast medium. There were no significant abnormalities. Similarly, ophthalmological examination did not reveal any pathological changes. Fluid in both pleural cavities and pericardial effusion was detected during diagnostic procedures. Due to progression of dyspnea, the patient was admitted to the cardiological ward. Pleural and pericardial effusions did not increase and no conduction abnormalities were detected during the 24 hr monitoring of electrocardiographic recording. Based on those findings, surgical treatment was discharged.

Laboratory evaluation revealed elevated titer of antinuclear antibodies with homogenous pattern at immunofluorescence. Anti-topoisomerase I antibodies (Scl-70) were detected and low level of C3 component of complement were shown. It was accompanied by an increase in acute phase reactants [C-reactive protein 37 mg/l, erythrocyte sedimentation rate (ESR) 63 mm/h]. Antibodies against *Chlamydia trachomatis* were not found. Capillaroscopy evaluation indicated a possible early phase of SSc. High resolution CT of the chest did not disclose interstitial inflammation or fibrosis. Pulmonary function tests were normal. Ultrasound examination of the abdomen was also normal.

Gastroscopic examination was performed due to moderate normocytic anemia and a polyp-like structure was found in pre-pyloric region of the stomach. This finding suggested paraneoplastic syndrome and further diagnostics was performed. The patient was recommended to perform endoscopic ultrasonography in specialistic gastrological center. Malignancy was excluded. Administration of 16 mg/day of methylprednisolone was recommended. The patients were admitted to the hospital nine days later due to rapid progression of renal insufficiency with hyperkaliemia (serum creatine 4.01 mg/dl, potassium 7.9 mmol/l). She was treated with extracorporeal dialysis. Pathological evaluation of renal biopsy suggested vasculitis due to increased cellular infiltrations in wall of the arcus arteries in the kidneys. SSc was diagnosed eight months after the first admission to the hospital due to current disorder. In the same time, induration of skin and contractures of the fingers were presented. Cutaneous manifestations developed in a very short period and were rapidly progressive. Modified Rodnan skin score was 14 in a few days after the first indurations were discovered. Medication with intravenous cyclophosphamide was introduced. Cyclophosphamide was well tolerated and medication was continued in oral route. Cardiac insufficiency was improved [1 point in the New York Heart Association (NYHA) scale].

The patient required hospital treatment on average once every three months due to recurrent infections of the upper and lower respiratory tract, urinary tract and exacerbation of symptoms of SSc. The last hospitalization was four years after the first one. The patient's condition was severe. Symptoms and signs of SSc were exacerbated, including difficulties in opening the mouth, narrowing of the lips, numerous ulcers of the hands and feet, limitation

in movements of almost all joints, no pulse in the lower right limb was detectable, "pitting" edema of the lower legs were revealed. Skin involvement was massive (modified Rodnan skin score > 40). Clinical signs of respiratory and circulatory failure were visible. The patient required passive oxygen therapy > 16 hrs./day; a tendency to hypotension was observed. After stabilization of the patient's general condition, she was discharged home under the care of her family. A few months later, the patient died of sepsis during the subsequent admission to the other hospital.

DISCUSSION AND LITERATURE REVIEW

The term "ssSSc" is not precisely defined. It describes the occurrence of characteristic symptoms and signs for SSc in some internal organs of a patient without skin manifestations distinctive for the disease [8]. The definition of ssSSc does not specify cutaneous involvement. The specificity of single skin lesion and even cutaneous indurations for SSc is insufficient. Some of these symptoms and signs may occur in individuals suffering from other diseases (including scleroderma-like syndromes) and even in healthy people. For example, cutaneous vascular changes, telangiectasias or pigmentation (hyperpigmentation and vitiligo in form of so-called salt and pepper skin). Therefore, the diagnosis of ssSSc is based on the absence of sclerodactyly, i.e., thickening of the skin of the fingers with joint mobility difficulties and contractures [4]. If there is no sclerodactyly and there are no other skin changes specific to SSc, the diagnosis of ssSSc can be considered complete (type I), if there is no sclerodactyly, but there are other skin changes that may indicate SSc, the diagnosis of ssSSc is incomplete (type II). Patients with type I or type II ssSSc are assumed never to develop sclerodactyly. If scleroderma with contractures manifests itself after clinically confirmed involvement of internal organs (in a manner specific to SSc), the diagnosis is ssSSc type III. It can be diagnosed as SSc with delayed development of skin lesions. If sclerodactyly occurs, the lesion is considered complete, and if there are only other skin lesions, incomplete disease. The classification of forms of ssSSc is summarized in Table 1.

The presented classification is dynamic and a transformation from type I or II to type III during the clinical observation of the patient is common. At the present stage of knowledge, it is impossible to determine whether the ssSSc types have different pathogenetic mechanisms. We do not know what factors determine course of the disease, i.e., sequence of the involvement of the skin and internal organs, and the dynamics of the process. Unfortunately, the classification into ssSSc types is only descriptive and indicates the heterogeneity of the course of the disease and partially reflects its activity. Rapid and more severe course of the disease in a patient without cutaneous involvement cannot predict whether skin involvement may occur later (change from type I or II to type III) or simply the severe and unfavorable progression of the internal organ involvement does not give enough time for development of delayed skin manifestations. However, these considerations are only of a classification nature, because we do not know the therapeutic strategies applied in the patients in relation to the type of disease.

The most important is diagnosis of ssSSc, which can be difficult. This form of SSc is relatively rare. It is estimated that ssSSc occurs in approximately 1–10% of all SSc patients [4, 7, 8]. The currently recognized paradigm of the development of systemic autoimmune dis-

Table 1. Classification of systemic sclerosis sine scleroderma. Modified from [4]

Type	Description
Type I	Complete visceral scleroderma: patients with evidence of sclerodermatous involvement of an internal organ or organs and without any sign or symptom of skin involvement typical for systemic sclerosis. The Raynaud's phenomenon as a vascular abnormality can be presented. There is no skin involvement detectable during all observation period.
Type II	Incomplete visceral scleroderma: patients with evidence of sclerodermatous internal organ involvement and serum antibodies specific to the disease with cutaneous manifestations typical of systemic sclerosis other than skin thickening, i.e., without sclerodactyly during entire period of clinical observation.
Type III	With delayed cutaneous involvement: patients with evidence of internal organ involvement typical of the disease and no sign of cutaneous sclerodermatous involvement, at least when internal organ manifestation becomes overt (complete form), or no skin thickening signs, at least when internal organ manifestation becomes overt (in complete form).

eases assumes that in a genetically predisposed person, with the coexistence of environmental factors and the triggering factor or factors, asymptomatic autoimmunity develops. The disease enters the preclinical phase, and the disease can be detected or suspected. The last stage is the phase of clinically overt systemic autoimmune disease. This is a working hypothesis of the pathogenesis of the discussed disorders, including SSc.

The diagnosis of SSc in advanced symptomatic patients with hardening of the skin and involvement of internal organs is relatively easy. Diagnosis at an early stage of the disease can be difficult. Previous classification criteria developed by the American Rheumatism Association (ARA) [10] or Le-Roy and Medsger [11] assumed the presence of skin induration as a condition for diagnosis. In patients who do not manifest the sign, the diagnosis is sometimes delayed, and at the time of diagnosis, organ changes are often significantly advanced.

The occurrence of Raynaud's phenomenon seems suggestive; however, apart from its high sensitivity (99.4%), it is characterized by very low specificity (4.2%) [12]. It can be a harbinger of various autoimmune diseases. It limits diagnostic value of Raynaud's phenomenon. The phenomenon occurs several years before the first SSc symptom other than Raynaud's phenomenon appears in patients with limited form of SSc, and 1–2 years in those with diffuse form of SSc [13, 14].

Koening et al. [15] showed that 54% of patients with Raynaud's phenomenon and with specific capillaroscopic findings and/or disease-specific antibodies developed the disease compared to 1.8% of patients without these prognostic factors. An increase in the number of diagnosed patients was due to the introduction of the strategy known as Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria. The criteria were selected with the Delphi method in a wide group of SSc experts [16]. There are three symptoms, called "red flags". They should raise suspicion of early phase of development of SSc, Raynaud's phenomenon, puffy fingers and ANA bodies [17]. In order to verify the diagnosis, it is also necessary to perform capillaroscopy and determine specific antibodies, i.e., anti-centromeric (ACA) and anti-topoisomerase I antibodies (Scl-70). Increased concentration of the antibodies is a predictor factor for the development of SSc [18].

The publication of new diagnostic criteria by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2013 was a significant progress facilitating diagnosis of the disease although the criteria were designed as classification criteria [19]. A retrospective analysis revealed that the introduction of the 2013 ACR/EULAR diagnostic criteria for systemic sclerosis compared to the 1980 ARA criteria allowed for an increase in the number of diagnosed cases. This means that, on average, 34.5% more patients can be classified into the limited SSc group, 31.6% more into the ssSSc group and 15.9% more into the pre-SSc group [19]. At the time of the diagnosis of the reported patient, the VEDOSS criteria were in force, and the ACR/EULAR criteria had not yet been announced. Among the red flags in the patient, we observed only positive ANA antibodies. We showed the presence of anti-topoisomerase I antibody (Scl-70 antibody); however, the capillaroscopic picture was ambiguous. This raised the suspicion of undifferentiated connective tissue disease, mixed connective tissue disease, or early-onset systemic sclerosis. Due to an exophytic gastric lesion, we started a parallel differential diagnosis for paraneoplastic syndrome. This syndrome is defined as a set of symptoms resulting from the occurrence of cancer, which may more or less resemble an autoimmune disease [20]. Lazzaroni et al. [21] showed that in people with positive anti-topoisomerase III antibodies at the time of diagnosis, there is an increased risk of cancer co-occurrence, which necessitates regular check-ups every 2–5 years. Moreover, in the patient we observed exudative serositis — fluid was found in both pleural cavities and in the pericardium [22]. Losada et al. [23] who studied a group of 92 people, 1/3 of the whom were eventually diagnosed with cancer, emphasized that the pleura and pericardium are the most frequently affected serous membranes, and the next most common causes of exudation were infections and autoimmune diseases. It was also noted that the presence of antinuclear antibodies was strongly associated with the final diagnosis of autoimmune disease, especially systemic lupus erythematosus [23]. Due to persistently elevated parameters of inflammation, suspicion of an oncological disease and serositis, it was not decided to start immunosuppressive treatment; however, glucocorticosteroid therapy was initiated. On the basis of endoscopic ultraso-

nography and histopathological examination, atypical hyperplasia of the gastric lesion was excluded.

Shortly after discharge from the hospital, the patient was readmitted due to acute renal failure. Kidney involvement in the course of ssSSc is twice as common as in patients with diffuse form of SSc [24, 25]. Renal failure may appear suddenly as scleroderma renal crisis (SRC) observed in less than 5% of cases [25], or chronic renal failure may develop over the course of the disease. SRC is associated with rapid deterioration of renal function with normal or elevated blood pressure up to severe hypertension. It has been proven that glucocorticoides may provoke SRC, especially use of higher dosages of steroids (> 15 mg).

Glucocorticosteroids inhibit the production of prostacyclin and increase the activity of angiotensin converting enzyme, which in patients with systemic sclerosis can lead to SRC [33]. This is due to the presence of risk factors in this group of patients, such as fibrosis or vasculopathy, which lead to the activation of the renin–angiotensin–aldosterone axis. As a result, we observe glomerular ischemia and the development of renal failure [33]. That is the reason why pulses of methylprednisolone were not administered in the patient.

Other predictive factors of occurrence of SRC are duration of disease progression < 3–5 years, cardiovascular pathologies (recent cardiac event, pericarditis, left ventricle failure), anemia of recent onset, anti-RNA polymerase III antibodies. Interesting thing is that diffuse skin damage or rapid progression of skin damage may precede the onset of kidney failure.

Renal function is assessed according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification. Acute failure is defined as an increase in creatinine concentration > 50% compared to the value determined in the last 7 days or an increase in creatinine concentration ≥ 0.3 mg/dl within 48 hours. If the blood pressure is normal, as it was in the reported case, diagnosis of SRC requires additionally to elevated creatinine at least one of the following criteria: proteinuria ≥ 2+ on a dipstick test, hematuria ≥ 2+ on a dipstick test, or ≥ 10 erythrocytes in the microscopic visual field, thrombocytopenia < 100,000/mm³, hemolysis defined as anemia less likely to have another cause and evidence of schizocytes and/or other red cell fragments, or enhanced reticulocytosis as well as pathologic findings in a kidney biopsy indicating SRC (Tab. 2).

Table 2. Predictive factors of occurrence of scleroderma renal crisis. Adapted according to Steen [28]

Diffuse skin damage
Rapid progression of skin damage
Duration of disease progression < 3–5 years
Recent cardiac event
• pericarditis • left ventricular failure
Anemia of recent onset
Anti-RNA polymerase III antibodies
Prednisone treatment > 15 mg/day within the last 3 months

The patient met 3/5 of the criteria, clinical symptoms and results of laboratory tests as well as history of a long-lasting medication with glucocorticoids was sufficient for diagnosis of SRC in a patient with ssSSc.

The factors of poor prognosis in the patient were age of the onset of the SRC > 53 years, normal blood pressure and the need for dialysis from the moment of diagnosis [26]. Treatment includes angiotensin-converting enzyme inhibitors (ACEIs) and plasmapheresis, and most patients require chronic therapy. Steen et al. [27, 28] in a group of 108 patients showed better one-year (76%) and five-year (66%) survival rates in patients treated with ACEI compared to survival (15% and 10% respectively) in the group of patients without ACEI treatment. It is not recommended to administer ACEIs in the prevention of renal crisis. Prevention with ACEIs is ineffective and is associated with a more severe course of SRC and worse prognosis due to the worse prognosis [25].

To date, only a few cases of patients with SSc have been described who did not develop skin induration at the time of SRC. In the majority of those patients, skin manifestations progressed rapidly after an episode of acute renal failure [4] .

When talking about antihypertensive drugs, it is important to emphasize the role of dihydropyridine calcium channel blockers (CCBs), the most important of which is nifedipine. These drugs can be successfully used in individuals with systemic sclerosis and diagnosed hypertension. An additional advantage is their vasodilatation mechanism, which explains why nifedipine remains a drug of choice in the treatment and prevention of Raynaud's phenomenon and finger ulcers. Researches shows a significant

reduction in the intensity and frequency of Raynaud's symptoms in individuals using CCBs, and the effectiveness is proportionally dependent on the drug dosage [34]. Due to normotension and the absence of Raynaud's phenomenon before establishing a diagnosis and the occurrence of SRC, CCBs were not administered to the patient.

Valentini et al. [29] emphasized that the involvement of internal organs occurs at an early stage of the disease, and sometimes even in the asymptomatic, preclinical phase. A study of 1632 patients reported by Trapiel-la-Martinez et al. [30] revealed that in patients who meet the VEDOSS criteria, gastrointestinal symptoms are present at an early stage of the disease, and the gastrointestinal involvement is an independent risk factor for progression of the disease.

In the presented case, the progression of the disease was not characteristic of SSc. In the early stage of the disease, there are no gastrointestinal symptoms or signs, no abnormalities in pulmonary function tests. Both cardiac involvement and interstitial lung disease developed later. Cutaneous involvement developed within 10 months after diagnosis of the disease and appeared after SRC.

The extent of skin involvement is associated with damage to internal organs. According to Nishimagi et al. [31], in patients who develop cutaneous involvement with a score of > 15 according the modified Rodnan skin score within a year of the onset of the first symptom other than Raynaud's phenomenon, the disease should be considered as a rapidly progressive form.

Systemic sclerosis, its organ complications and immunosuppressive treatment contribute to increased morbidity of patients. Common pathogens, usually responsible for mild infections in healthy human beings, can cause a serious infection in patients with autoimmune disorders. Investigation of a large cohort of hospitalized SSc patients showed that the most common and serious infections were: pneumonia (45%), sepsis (32%), soft tissue infection (19%), urinary tract infection (3%) and opportunistic infections (3%) [32]. Our patient systematically required hospital admissions due to recurrent infections, especially in the respiratory tract. She died of sepsis in another hospital.

CONCLUSION

It should be noted that SSc is a disease with a very heterogeneous course. A small proportion of patients do not have skin involvements (during the course of the disease or only at the beginning of the overt disease), and it is responsible for difficulties in establishing the final diagnosis. It should be remembered that the suspicion of an autoimmune disease is often associated with administration of glucocorticoids. Such therapy in patients with ssSSc may increase the risk of SRC. Renal failure is also often the first symptom of ssSSc. The role of capillaroscopic examination and the determination of autoantibodies specific to SSc should be mentioned. However, it is important to remember the possibility of developing ssSSc, and the need for a comprehensive diagnosis of the disease based on group of indices only.

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