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Rapidly progressive systemic sclerosis with a fatal outcome in male patients

Postępująca twardzina układowa o niepomyślnym przebiegu u mężczyzn

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Key words: systemic sclerosis, prognostic factors.

Słowa kluczowe: twardzina układowa, czynniki prognostyczne.

Summary

Objectives: Retrospective analysis of clinical outcomes of male patients with particularly severe and rapidly progressive diffuse systemic sclerosis (SSc) with a fatal outcome with emphasis on organ involvement and results of diagnostic tests, and tentative distinction of a subgroup of especially progressive SSc.
Material and methods: In the last few years among patients with SSc hospitalized in our centres, five patients with particularly rapidly progressive disease were distinguished. Despite aggressive treatment, the disease led to a fatal outcome in a short time. Their clinical history and results of diagnostic tests were evaluated.
Results: All of them were smokers and three of them did not stop smoking after the diagnosis. Laboratory findings revealed high titres of Scl70 antibodies and enhanced erythrocyte sedimentation rate (ESR) in all of the patients. Most of them had increased serum creatine kinase (CK) values. During the disease rapidly progressive severe organ involvement was observed (pulmonary fibrosis, renal failure, cardiac failure, pulmonary arterial hypertension). The skin thickening increased rapidly and they died within 12-24 months after the first signs of skin thickening. Acute cardiac failure was the cause of death.
Conclusions: The described cases suggest possible distinction of a subset of a subgroup of patients with a particularly severe and

Streszczenie

Cel pracy: Analiza retrospektywna wyników badań w grupie mężczyzn chorych na twardzinę układową o wyjątkowo ciężkim przebiegu, zakończoną zgonem w krótkim czasie od rozpoznania, ze szczególnym uwzględnieniem wyników badań laboratoryjnych i obrazowych jako próba wyodrębnienia podgrupy chorych o agresywnym przebiegu twardziny.
Materiał i metody: Na przestrzeni ostatnich kilku lat wyodrębniono grupę pięciu chorych hospitalizowanych w naszych ośrodkach, u których przebieg choroby był wyjątkowo agresywny i w krótkim czasie doprowadził do zgonu. Oceniano przebieg choroby, wyniki badań laboratoryjnych i obrazowych.
Wyniki: Przeanalizowano wyniki badań 5 mężczyzn w wieku 35–62 lat, chorych na twardzinę układową o wyjątkowo szybkim i ciężkim przebiegu zakończoną zgonem. Wszyscy badani byli palaczami tytoniu, przy czym 3 nie zaprzestało palenia w trakcie choroby. U wszystkich pacjentów stwierdzono: występowanie przeciwciał Scl70 i przyspieszony OB. U większości z nich stwierdzono zwiększoną aktywność CPK. W czasie choroby obserwowano szybkie postępujące istotne zajęcie narządów wewnętrznych (włóknienie płuc, niewydolność nerek, niewydolność krążeniowo-oddechową, nadciśnienie płucne). U wszystkich chorych stwierdzono szybkie narastanie zmian skórnych. Chorzy zmarli w ciągu 12–24 miesięcy od wystąpienia zmian skórnych.

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rapidly progressive disease. It might be a population of patients with the following characteristics: males over 40 years of age with high titres of anti-Scl70 antibodies and elevated serum CK levels. This is consistent with the presently published data on factors associated with fatal prognosis in patients with SSc.

Przyczyną śmierci u opisywanych pacjentów była ostra niewydolność krążeniowo-oddechowa.

Wnioski: Opisane przypadki sugerują istnienie podgrupy chorych o wyjątkowo szybko postępującym rozwoju choroby, być może jest to odrębna populacja chorych o następującej charakterystyce: mężczyźni po 40. roku życia, palacze, u których stwierdzono duże miano przeciwciał Scl70 i zwiększoną aktywność CPK. Jest to zgodne z dotychczasowymi danymi literaturowymi wskazującymi na czynniki niepomyślnego rokowania u chorych na twardzinę układową.

Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disorder characterised by progressive fibrosis of the skin and subcutaneous tissue, occurrence of Raynaud's phenomenon and other vascular abnormalities as well as internal organ involvement due to fibrosis, especially within the lungs, heart, kidneys and alimentary tract [1-3]. It affects females much more often than males [2, 3] but the disease prognosis is worse in males [4]. The course of the disease and its severity have various clinical characteristics, from a relatively benign condition to a rapidly progressive disease with a high risk of mortality [5, 6]. The disease duration may also vary from months to decades [7]. The prevalence and type of organ involvement depend mainly on the subtype (limited, diffuse) of the disease. Limited SSc is characterized by the occurrence of anti-centromere antibodies and thickening of skin distal to the elbows and knees. Diffuse cutaneous SSc is characterized by the occurrence of anti-Scl70 antibodies and the presence of skin thickening proximal to elbows and knees. Pulmonary fibrosis and pulmonary arterial hypertension are the leading causes of morbidity in patients with SSc [4, 5, 8, 9].

Objectives

Retrospective analysis of clinical outcomes of five male patients with particularly severe and rapidly progressive diffuse SSc with a fatal outcome with emphasis on organ involvement and results of diagnostic tests.

Material and methods

In the last few years among patients with SSc hospitalized in our centres, five patients with particularly rapidly progressive disease were distinguished. Despite aggressive treatment, the disease led to a fatal outcome in a short time. Their clinical history and results of diagnostic tests were evaluated.

Analysed patients were males with diffuse systemic SSc diagnosed according to the American College of Rheumatology classification criteria.

The extent of skin involvement was evaluated with modified Rodnan skin score (mRs) (the result presented in the paper is the result measured during the last hospitalization of the individual). ANA, anti-Scl70 and anti-centromere antibodies were detected using an ELISA test. Organ involvement was diagnosed on the basis of symptoms and the results of diagnostic tests. Pulmonary involvement was defined as bibasilar pulmonary fibrosis revealed on HRCT scan. Renal involvement was defined as age-related creatinine clearance <80 ml/min, proteinuria. Cardiac involvement was defined as palpitations, conduction disturbances, ventricular arrhythmia, heart failure or persistent pericardial effusion detected by echocardiography. Myositis was defined as increased CK serum levels, changes in electromyography (EMG) and concomitant muscle weakness. Articular involvement was defined as synovitis and swelling with or without tenderness to palpation. Oesophageal involvement was defined as dysphagia, odynophagia or intermittent heartburn and was investigated by barium swallowing. Intestinal involvement was defined as bowel disturbances, and evaluated by colonoscopy. Pulmonary hypertension was defined as systolic pulmonary arterial pressure (sPAP) > 35 in colour Doppler echocardiography. History of smoking was also evaluated. All of the patients were treated with pulses of cyclophosphamide (1000 mg/4 weeks). Two of them were treated with low doses of prednisone orally. All of them were treated with an angiotensin-converting enzyme (ACE) inhibitor and a proton pump inhibitor.

Results

First skin symptoms of SSc appeared after the age of 50 in four of the patients. One patient was 35 years old at the time of the first skin symptoms. All of them were smokers and three of them did not stop smoking after the recognition of SSc diagnosis. Laboratory findings revealed positive Scl70 antibodies, negative anti-centromere antibodies and increased acute phase reactants (ESR, C-reactive protein – CRP) in all of the patients. Most of them had increased CK values. During the disease rapidly progressive severe organ involvement was

observed. It included: progressive pulmonary fibrosis, cardiac involvement, pulmonary arterial hypertension, intestinal and oesophageal involvement, and renal involvement (table I). The skin thickening increased rapidly in all of the patients to reach 28-42 mRs score at the last hospitalization, and they died within 12-24 months after the first signs of skin thickening had appeared. Acute cardiac failure was the cause of death. The results are presented in tables I and II.

Discussion

Compared to the general population the risk of death is increased in patients with SSc. In the currently published literature the mortality ratio in SSc ranges between 1.5 and 7.2 [3, 9]. Renal, cardiac and pulmonary involvement are considered as important predictors of mortality. The presence of anti-Scl70 antibodies is associated with an additional 1.3-fold increase in risk [7, 10]. In the currently published literature, investigators point to factors associated with poor prognosis in SSc. They include: diffuse skin involvement [4], male sex [4], older age at the onset of SSc [11], internal organ manifestations [6, 9], pigmentation disturbances, and nailfold capillary loss seen on capillaroscopy [11]. Anti-Scl70 antibodies, anaemia, increased ESR, increased CRP level, abnormal urine sediment, and proteinuria without scleroderma renal crisis are also considered as poor prognostic factors. Pulmonary hypertension and myositis were reported to be connected with poor prognosis [5]. Presence of anti-centromere antibodies is reported as a favourable prognostic factor [5, 6]. The results of the study conducted by Czirják *et al.* [6] provided evidence that a malignant disease diagnosed within four years after SSc had been diagnosed also caused a poor outcome. Simeon *et al.* [11] reported that in a group of 79 patients with SSc lung involvement, renal crisis and age at diagnosis over 60 years were the variables associated with decreased survival. Furthermore, the extent of skin

Table I. Organ involvement in the group of patients with rapidly progressive SSc with a fatal outcome
Tabela I. *Zmiany narządowe w grupie chorych na szybko postępującą twardzinę układową zakończoną w krótkim czasie zgonem*

Patient	Organ involvement	mRs	NYHA	Scl70	ACA
1	Pulmonary involvement: lung fibrosis, gradually increasing pleural effusion Cardiac involvement: progressive conduction disturbances, atrial fibrillation, Ventricular arrhythmia, pericardial effusion Oesophageal involvement: dysphagia Intestinal involvement: bowel disturbances Myositis, arthritis Skin hyperpigmentation	29	2	+	–
2	Pulmonary involvement: lung fibrosis Cardiac involvement: pericardial effusion Renal involvement: renal crisis Oesophageal involvement: dysphagia Myositis, arthritis	40	3	+	–
3	Pulmonary involvement: lung fibrosis Cardiac involvement: progressive conduction disturbances, atrial fibrillation Renal involvement: gradually increasing serum creatinine level, proteinuria Oesophageal involvement: dysphagia Intestinal involvement Myositis, arthritis	42	3	+	–
4	Cardiac involvement: progressive conduction disturbances, atrial fibrillation Renal involvement: gradually increasing serum creatinine level, proteinuria, Arterial hypertension Oesophageal involvement: dysphagia Intestinal involvement Myositis, arthritis	28	3	+	–
5	Pulmonary involvement: lung fibrosis Renal involvement: proteinuria, arterial hypertension Intestinal involvement Recurrent ulcerations of epiglottis	42	3	+	–

mRs – modified Rodnan skin score, NYHA – New York Heart Association classification of heart insufficiency, Scl70 antibodies, ACA – anticentromere antibodies

Table II. Clinical characteristics of the group of patients with rapidly progressive systemic sclerosis with a fatal outcome

Tabela II. *Charakterystyka kliniczna grupy chorych na szybko postępującą twardzinę, zakończoną w krótkim czasie zgonem*

Patient	Age at first skin symptoms [years]	Months from Raynaud onset to first skin symptoms	Months from first skin symptoms to death	Smoking	Did he stop smoking after the diagnosis?	CRP [mg/l]	ESR [mm/h]	CK [U/l]	Proteinuria	LVEF (%)	Lung fibrosis	PAH
1	62	86	24	yes	no	24	16	507	no	45	yes	yes
2	53	4	12	yes	no	50	49	500	yes	53	yes	no
3	50	10	16	yes	yes	79	77	2833	yes	45	yes	yes
4	55	no data	15	yes	no	72	27	300	no	46	no	yes
5	35	no data	24	yes	yes	56	78	98	yes	50	yes	yes

CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, CK – serum creatine kinase, LVEF – left ventricular ejection fraction, PAH – pulmonary hypertension

involvement is regarded as an important prognostic factor [4, 9, 11].

Evaluation of geographical differences of disease manifestations reported by authors analysing the EULAR Scleroderma Trials and Research (EUSTAR) group database revealed that eastern European centres care for patients with more severe SSc manifestations than the rest of Europe [12]. Another study analysing the EUSTAR database found that older age at onset of the disease and the presence of anti-Scl70 antibodies are independent risk factors for severe organ manifestations [2].

Conclusions

The described cases suggest possible distinction of a subset of a subgroup of patients with a particularly severe and rapidly progressive disease. It might be a population of patients with the following characteristics: males with older age at the onset of the disease with high titres of anti-Scl70 antibodies, increased acute phase reactants and elevated CK levels. History of smoking may contribute to acceleration of the course of the disease. This is consistent with the presently published data on the factors associated with fatal prognosis in patients with SSc.

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