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Everything you always wanted to know about systemic sclerosis but were afraid to ask: Part 1. Clinical pictures

ABSTRACT

The authors present the clinical picture of systemic sclerosis including organ and system involvement.

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KEY WORDS: systemic sclerosis; classification criteria; skin; interstitial lung disease; heart; gastrointestinal tract; kidneys

INTRODUCTION

Systemic sclerosis (SSc, scleroderma) is a systemic connective tissue disease that is marked by fibrosis of the skin and internal organs, vasculopathy, immunological disorders and the production of autoantibodies [1]. Systemic sclerosis can be divided into limited systemic sclerosis, diffuse systemic sclerosis, systemic sclerosis sine scleroderma. The clinical picture of the disease varies widely according to the degree of organ involvement. The course of the disease and prognosis also vary. Therefore, it is extremely important to diagnose scleroderma as soon as possible and implement appropriate treatment with organ-specific therapy. Making a diagnosis, especially in the early stages of the disease, is often problematic.

VEDOSS

In 2011, researchers from the EUSTAR group proposed the concept and criteria of VEDOSS — very early diagnosis of SSc. Experts presented potential manifestations to guide rheumatologists in the diagnosis of early scleroderma:

1. Presence of Raynaud's phenomenon;
2. Swollen fingers;
3. Presence of specific antibodies:
— ACA (anti-centromere antibodies),
— Scl-70 (anti-topoisomerase-I antibodies),
— or anti-RNA polymerase III antibodies;
4. Microcirculatory disturbances as reflected by capillaroscopy (Tab. 1) [2].

However, the presence of Raynaud's phenomenon itself, swollen fingers, and antinuclear antibodies (ANA) was defined as "red flags" that give rise to a strong suspicion of very early systemic sclerosis [2]. Therefore, capillaroscopy and broadening of the ANA antibody panel are necessary in these patients to detect antibodies typical for scleroderma. It is also important to bear in mind that other types of antibodies may occur in the course of SSc. For example, anti-PM-Scl and anti-Ku antibodies rarely accompany systemic sclerosis, however, they may be associated with an increased risk of cancer development in patients.

CLASSIFICATION CRITERIA

The first classification criteria for SSc, dating back to 1980 and consisting of major criteria

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Table 1. Scleroderma-type capillaroscopic pattern (according to Cutolo [6])

Characteristic	Scleroderma-type pattern early pattern	Scleroderma-type pattern active pattern	Scleroderma-type pattern late pattern
Reduced capillary count (density)	Absent	Present	Present
Megacapillaries	Present	Present	Absent
Extravasations (petechiae with a cap-like appearance)	Commonly present	Commonly present	Absent
Abnormal capillary morphology	Absent	May be present	Present

such as skin induration and minor criteria such as sclerodactyly, digital pitting scars, or interstitial lesions at the level of lung bases were not perfect. Those criteria mainly applied to patients with a long history of scleroderma and did not include patients with early-stage disease or many patients with a limited form of the disease — according to some authors, even up to 20% of patients [3]. Therefore, many patients remained undiagnosed and without appropriate treatment.

In 2013, new classification criteria were announced by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) [4]. The new criteria demonstrate greater sensitivity and specificity compared to the criteria from 1980. They are based on three basic clinical manifestations typical of scleroderma: skin and/or internal organ fibrosis, the presence of typical antibodies, and vascular damage (vasculopathy), which has led to the significant role of nailfold capillaroscopy. The criteria are shown in the summary Table 2 [4]. Systemic sclerosis can be diagnosed if the total score is ≥ 9 points. The criteria do not apply to patients with skin induration sparing the fingers or with diseases resembling scleroderma, such as nephrogenic systemic fibrosis, eosinophilic fasciitis, graft-versus-host disease, porphyria, mucinous oedema, erythromelalgia, lichen sclerosus, and others.

Systemic sclerosis can be classified into the following clinical forms:

— limited systemic sclerosis (lSSc), previously known as the CREST syndrome. Skin induration affects the face and distal parts of the upper and lower limbs in relation to the elbow and knee joints. Skin lesions develop relatively slowly, and Raynaud's phenomenon usually precedes the onset of other manifestations by many years. In this form of SSc, the most commonly affected internal organ is the digestive tract, especially the esophagus, followed by interstitial lung disease (ILD). The heart is relatively rarely affected, whereas pulmonary arterial hypertension and primary biliary cirrhosis of the liver are more common than in diffuse systemic sclerosis [5];

— diffuse systemic sclerosis, characterised by skin lesions affecting the face, proximal parts of the upper and lower limbs, and trunk. The course of the disease is usually more severe and rapid compared to the limited form of systemic sclerosis. Raynaud's phenomenon typically occurs concurrently with skin induration or later. The later it occurs, the worse the prognosis regarding disease severity. The lungs are most commonly affected (ILD), followed by the digestive tract, then the heart and kidneys [5];

Table 2. Classification criteria for systemic sclerosis according to ACR/EULAR (2013)

Classification criteria for systemic sclerosis according to ACR/EULAR (2013)	
	Criteria score
Induration of the skin of both hands proximally from the metacarpophalangeal joints	9
Induration of the skin of the fingers Swollen whole fingers (oedema)	2
Sclerodactyly	4
Damage to fingertips Fingertip ulcers	2
Digital pitting scars	3
Teleangiectasias	2
Abnormalities of nailfold capillaries typical of systemic sclerosis	2
Pulmonary arterial hypertension and/or interstitial lung disease	2
Raynaud's phenomenon	3
Autoantibodies specific to systemic sclerosis: — anti-centromere antibodies — anti-topoisomerase I antibodies — anti-RNA polymerase III antibodies	3

Interpretation: systemic sclerosis can be diagnosed if the total score is ≥ 9 points

— systemic sclerosis *sine* scleroderma — lesions typical of internal organ scleroderma, serological changes without skin lesions [5];
— overlap syndromes — clinical manifestations of scleroderma overlap with manifestations of another systemic disease, such as rheumatoid arthritis or dermatomyositis [5];
— some authors also include early scleroderma as a clinical form of SSc, which is also referred to as high-risk syndrome for SSc.

ORGAN LESIONS

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is a condition where there is an episodic discoloration of the fingers, toes, nose, or earlobes due to exposure to cold temperature or emotional stress (sometimes without any apparent cause). It is the most common manifestation of SSc, affecting up to 96% of patients. It may precede the onset of organ involvement, particularly lSSc, by many years.

The phase specificity of Raynaud's phenomenon is characteristic:

1. Blanching phase (white phase) caused by the constriction of small blood vessels.
2. Cyanosis phase (blue phase) caused by the accumulation of deoxygenated blood in the vessels of the subpapillary plexus.
3. Active hyperemia phase (red phase), which is the subsequent reddening, swelling, and often a burning sensation.

In the differential diagnosis, other causes of Raynaud's phenomenon should always be considered, such as other systemic connective tissue diseases, myeloproliferative and lymphoproliferative disorders, neoplasms, hand-arm vibration syndrome, compression syndromes, or drug-induced changes, e.g. during the use of ß-blockers, cytostatics or oral contraceptives.

The key additional examination is nailfold capillaroscopy, as shown in Figures 1 and 2. Typical capillaroscopic changes observed in SSc patients include the presence of giant capillaries — megacapillaries, reduced total number of vessels with areas of avascularity, and characteristic extravasations known as petechiae with a cap-like appearance. According to Cutolo [6], early, active, and late phases of capillaroscopic changes are distinguished. In the late phase, branched pattern of vascular loops with signs of neoangiogenesis are also often found.

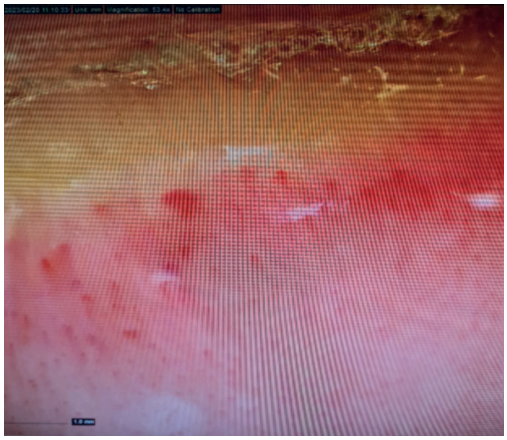

Figure 1. Nailfold capillaroscopy in a patient with systemic sclerosis (visible megacapillaries)

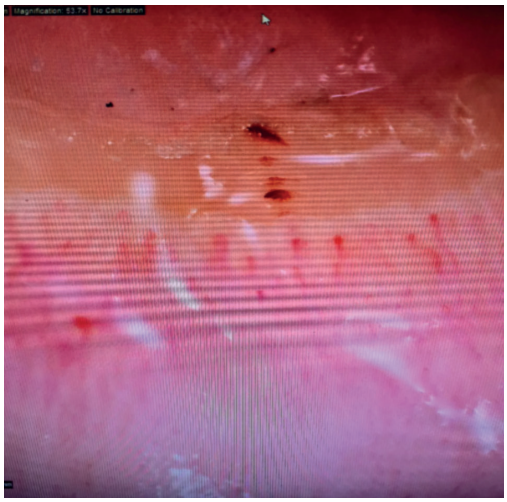

Figure 2. Nailfold capillaroscopy in a patient with systemic sclerosis (visible petechiae with a cap-like appearance)

SKIN INVOLVEMENT

Skin, except in the form of scleroderma without induration of the skin, is almost always affected by the disease process. Although there are many serious skin lesions such as open sores (ulcers) and depigmentation, skin involvement is not *per se* associated with increased mortality in SSc. However, the degree of skin involvement and the rate of progression of skin lesions are closely related and correlate with the degree of internal organ involvement and the risk of mortality [7, 8]. Induration of the skin, the most common manifestation of SSc, consists of three phases of skin lesions: from the edematous phase through the indurative phase to the atrophic phase. This is best seen in the example of the skin on the fingers. In the edematous phase, the fingers are puffy (see Fig. 3 and 4), then the indurated skin makes

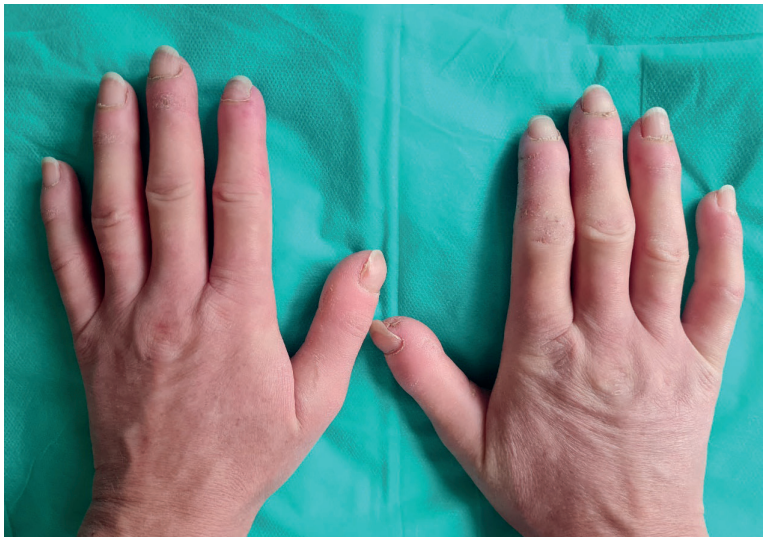

Figure 3. Cutaneous lesions of the hands in the course of systemic sclerosis (puffy fingers)

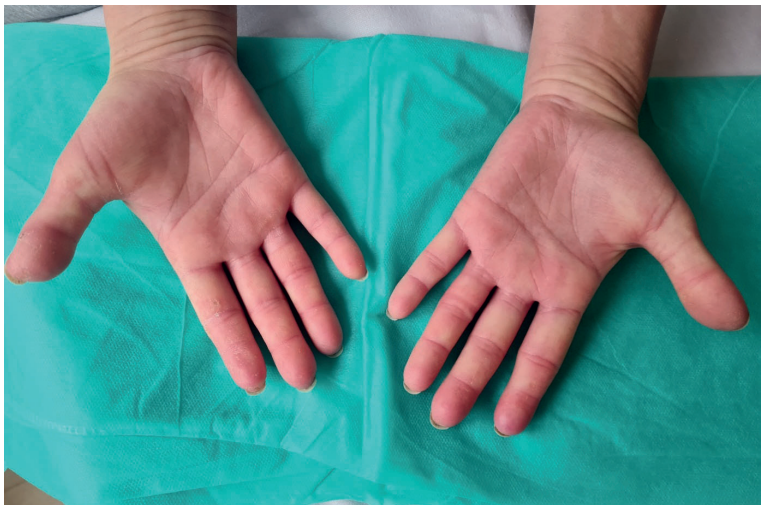

Figure 4. Cutaneous lesions of the hands in the course of systemic sclerosis (puffy fingers)

it impossible to control the fingers in flexion and extension — the impression of a "tight glove", and finally there are atrophic skin lesions.

The currently recommended scale for assessing skin involvement (extent of lesions and degree of skin induration) is the modified Rodnan Skin Score (mRSS) [9]. The examination involves a palpation-based assessment of skin induration in 17 areas of the body: face, fingers of both hands, both palms, forearms, upper arms, anterior chest, abdomen, both feet, lower legs, and thighs. Three degrees of skin induration are distinguished, ranging from 0 to 3. Degree 0 represents normal skin texture, where the skin can be easily grasped and forms a fold, while degree 1 indicates mild skin induration, degree 2 denotes moderate skin induration, and degree 3 indicates severe skin induration. The maximum score on the Rodnan scale is 51 points (Fig. 5).

Typical skin lesions in the course of SSc also include hyperpigmentation, salt-and-pepper appearance of the skin (Fig. 6), digital pitting scars, and telangiectasias, especially on the face and décolleté area of lSSc patients. Telangiectasias are a specific reflection of microcirculation abnormalities [10]. The massive and rapid appearance of new telangiectasias correlates with the progression of vascular lesions (pulmonary hypertension, fingertip ulcers).

Fingertip ulcers are observed in nearly 50% of patients diagnosed with SSc and they usually appear within the first five years of the disease [10]. Finger ulcers are painful and significantly reduce the quality of life of patients. In the group of patients meeting the VEDOSS criteria, ulcers

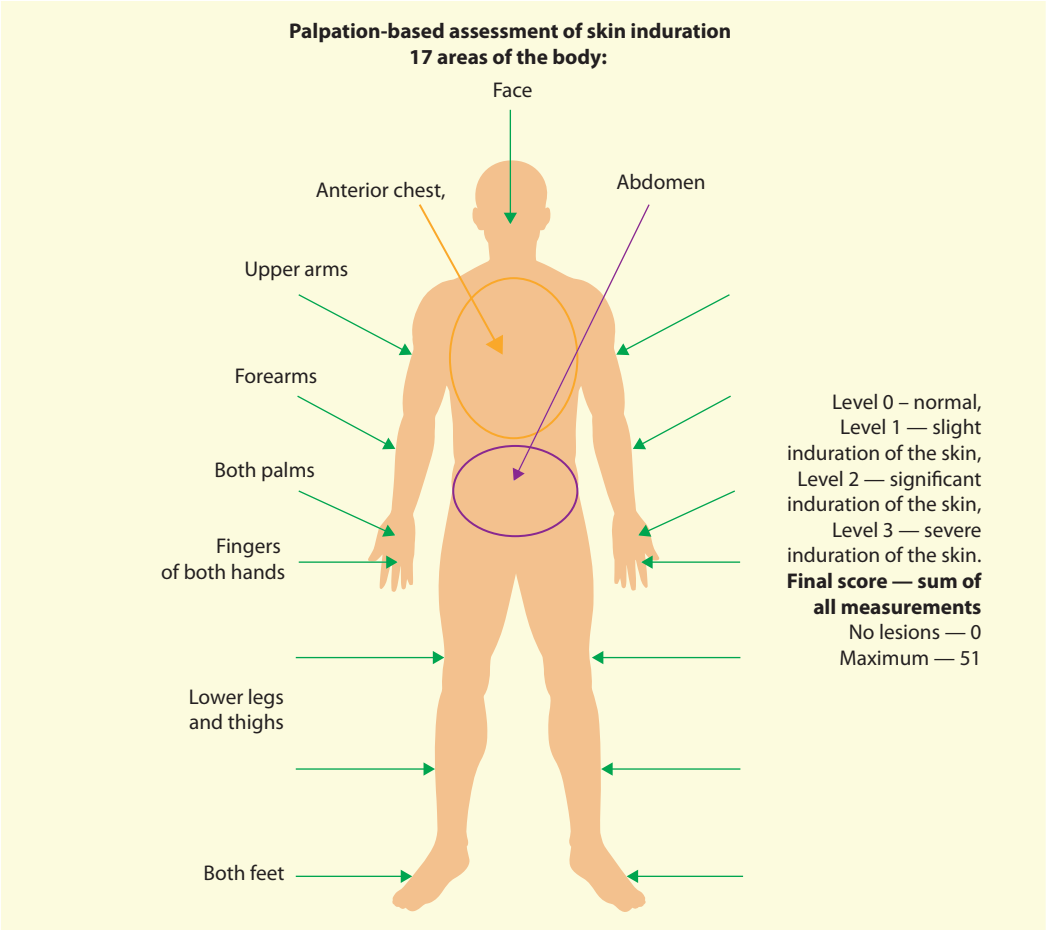

Figure 5. Rodnan score

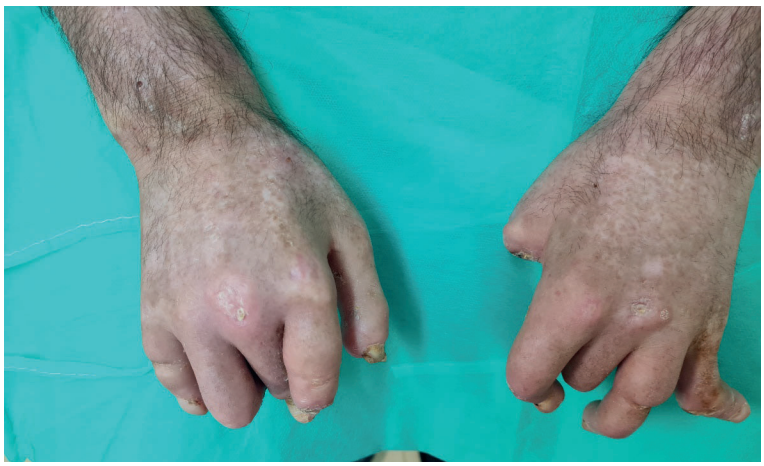

Figure 6. Abnormal pigmentation of the skin on the hands in the form of salt-and-pepper appearance in the course of systemic sclerosis, as well as finger contractures and a history of self-amputation of phalanges

were observed in patients with lung and/or gastrointestinal involvement, while they were not found in patients without internal organ involvement. Researchers from the EUSTAR group classified finger ulcers into episodic, recurrent, and chronic. The most problematic ulcers are infected ones (particularly those caused by *Staphylococcus aureus*), which can often lead to *osteomyelitis* and finger amputations (see Fig. 6).

In some patients, calcifications are also found within the skin [11], especially in the area of the fingers, knee joints, and elbow joints. Large skin calcifications in SSc are called Thibierge–Weissenbach syndrome.

Symptoms affecting the joints and muscles are also extremely significant, troublesome, and often difficult to treat. Key symptoms include joint pain and inflammation, particularly in the small joints of the hands, similar to rheumatoid arthritis. Tendon friction rubs, which are an independent factor for poor disease prognosis, are also often encountered [12].

Myositis is a fairly common but not always encountered manifestation reported by SSc patients [13]. Patients mainly complain of weakness of the muscles and pain — usually in the proximal muscles of the upper and lower limbs. Increased creatine kinase activity in the blood serum and myogenic electromyogram (in electromyography) are found in additional examinations. Magnetic resonance imaging is important in imaging of inflammatory changes in the muscles. Unlike polymyositis, skin and muscle biopsy is not recommended for histopathological examination in SSc patients.

As for the immunological profile, myositis-associated autoantibodies are usually found in these patients [14]. These are mainly PM/Scl antibodies (found in 3–13% of patients) and anti-Ku antibodies (found in 1–5% of patients). It should be remembered that the treatment approach for patients with *sclero-myositis* or overlap syndrome differs slightly from the therapeutic management for SSc patients without myositis.

INTERSTITIAL LUNG DISEASE

Abnormal high-resolution computed tomography (HRCT) images of the lungs are found in more than 85% of SSc patients (Fig. 7), and changes in respiratory function tests are found in 45-100% of SSc patients, of whom 25–41% have typical restrictive disorders with a decrease in forced vital capacity (FVC), total lung capacity and with impaired diffusing lung capacity for carbon monoxide (DLCO) — the term TLCO (transfer factor of the lung for carbon monoxide) is now used [15].

Isolated reductions in diffusing lung capacity occur in 18–47% of patients with ILD — it should be noted that these reductions are also found in isolated pulmonary hypertension [15].

Histopathological examination of lung sections from SSc patients is dominated by non-specific interstitial pneumonia. Only 8% of patients present with usual interstitial pneumonia. Cryptogenic organising pneumonia and alveolar haemorrhage are occasionally found [16].

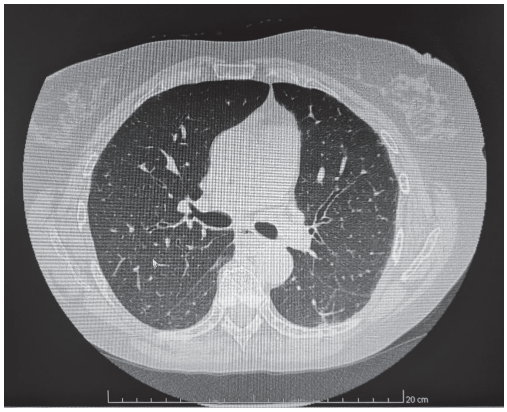

Figure 7. Interstitial lung lesions in the course of systemic sclerosis as seen on HRCT scans

The histological picture of the lesions does not affect the prognosis. On HRCT images, pulmonary alveolitis and interstitial tissue inflammation have initially a milk-glass appearance, which is followed over time by interstitial fibrosis in the form of small nodules, reticulum — a honeycomb-like structure.

Bronchoalveolar lavage examination accompanied by smear test is still controversial in the diagnosis of pulmonary lesions in SSc patients. There is often an increase in the percentage of eosinophils > 2.5% or neutrophils > 3% [17].

However, the 6-minute walk test is used in daily practice [18]. The clinical manifestations of ILD are non-specific: initially there is dyspnea on exertion, while in the advanced form of the disease there is dyspnoea at rest, a chronic dry cough and often pleuralgia.

Risk factors for the onset and progression of ILD include diffuse SSc (especially the early stage), male sex, the presence of anti-topoisomerase I antibodies and FVC% < 70% [16]. Distler et al. proposed a definition for the progression of ILD in SSc. Diagnosis of progression is based on a decrease in FVC ≥ 10% or a decrease in TLCO ≥ 15%, but also on a decrease in FVC of 5–9% with a concomitant decrease in TLCO ≥ 15% [16].

CARDIAC INVOLVEMENT

Cardiac involvement is a common cause of death in SSc patients. Autopsy findings include a variety of lesions: myocardial fibrosis, including electrical conduction system of the heart, myocarditis, pathologies within the valvular apparatus of the heart, and pericardial lesions [19]. The problem of cardiac Raynaud's phenomenon is also often discussed. The presence of impaired myocardial blood supply in

response to low temperature or exercise and in the absence of concomitant coronary artery pathology was proven by single photon emission computed tomography [20]. The range of clinical manifestations indicative of cardiac involvement is wide. They range from asymptomatic conduction abnormalities, symptomatic ventricular or supraventricular arrhythmias, valvular defects, fluid in the pericardial sac to acute heart failure and rampant myocarditis. The patient usually reports dyspnoea, palpitation or chest pain.

The basic diagnostic test is resting electrocardiography (12 leads), 24-hour Holter electrocardiography recording and transthoracic echocardiography [21]. Many SSc patients were diagnosed with left ventricular dysfunction — most often diastolic, less often systolic — but also right ventricular dysfunction. When pulmonary hypertension is suspected based on echocardiography, it is necessary to extend the diagnostic evaluation by performing right heart catheterization. Coronary angiography is also often necessary [20]. Between 5–16% of SSc patients have clinically manifested pericardial involvement. It is mainly pericarditis with fluid in the pericardial sac while pericardial tamponade or constrictive pericarditis are less common [22]. Magnetic resonance imaging is a test that best illustrates inflammatory changes in the myocardium [23]. There are cases where myocardial biopsy is also necessary.

Biochemical indices such as serum creatinine kinase activity, troponin I levels and N-terminal pro-brain natriuretic peptide (NT-proBNP) peptide levels are extremely useful, readily available markers of cardiac damage in SSc. Troponin I is more recommended than troponin T, especially in patients with skeletal muscle involvement. This is because troponin I is more specific to the myocardium. NT-proBNP levels have a prognostic role in patients with pulmonary hypertension. High serum NT-proBNP levels correlate with increased mortality in SSc patients [24].

PULMONARY HYPERTENSION

Pulmonary hypertension is diagnosed by right heart catheterization. It is diagnosed when the mean pulmonary artery pressure is ≥ 25 mm Hg at rest. However, in 2018, this value was proposed to be reduced to > 20 mm Hg [25]. The criterion for exercise-induced pulmonary hypertension — an increase in mean pulmonary pressure > 30 mm Hg during exercise — is no longer used in clinical practice.

Pulmonary arterial hypertension (PAH) occurs in 3–12% of SSc patients and is a very serious complication of the disease. Clinical manifestations are very uncharacteristic as dyspnoea and increased fatigue predominate. PAH is associated with ongoing inflammatory lesions within the endothelium of small pulmonary vessels, increased fibrosis, and obliteration of vessels [26]. Pulmonary hypertension may also be secondary to interstitial lung lesions. PAH is more commonly seen in patients with the limited form of systemic scleroderma, with the presence of anti-centromere antibodies, with multiple telangiectasias and in patients with a long history of Raynaud's phenomenon [7].

Transthoracic echocardiography is the primary, non-invasive, and widely used test for the diagnosis of pulmonary hypertension. However, echocardiography only assesses the likelihood of pulmonary hypertension. An important parameter is the tricuspid regurgitant jet velocity (TRJV) on Doppler examination. If TRJV is > 2.8 m/s (tricuspid valve gradient ≥ 31 mm Hg), the probability of pulmonary hypertension is considered intermediate, while if TRJV on Doppler examination is > 3.4 m/s (tricuspid valve gradient > 45 mm Hg), the probability of pulmonary hypertension is considered high. It is also important to consider other features of right ventricular strain [27].

The diagnosis of pulmonary hypertension should be confirmed by direct tests of blood pressure and blood flow during pulmonary artery catheterisation [25].

An important additional test is also the measurement of diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO or TLCO). Great vigilance should be raised by a TLCO result < 60% without concomitant interstitial lung lesions, as well as a value of FVC%/TLCO% > 1.6. As mentioned in an earlier section, NT-proBNP levels have a prognostic role in patients with pulmonary hypertension.

GASTROINTESTINAL TRACT

Gastrointestinal involvement in SSc is estimated in up to 95% of patients. Virtually all sections of the gastrointestinal tract can be affected by the disease process.

The lesions already affect the initial section of the gastrointestinal tract, i.e. the oral cavity. Many patients have difficulty opening their mouth (trismus), dry mouth (xerostomia), gingivitis or, finally, tooth decay. Functional and morphological abnormalities of the

esophagus occur in 75–90% of SSc patients [28]. Motility disorders mainly affect the lower part of the esophagus — lower esophageal sphincter tone reduction. Dysphagia, heartburn, regurgitation, chest pain, and complications of aspiration are common symptoms with which a patient presents to the doctor.

Erosive esophagitis, Barrett's esophagus and esophageal adenocarcinoma are also quite common in the course of SSc [29].

The stomach is affected by pathological process in approximately 50–60% of SSc patients. These are mainly lesions in the form of motility disorders (gastroparesis), mucosal damage, vascular lesions in the form of telangiectasia including gastric antral vascular ectasia (GAVE), also known as watermelon stomach. These lesions often lead to upper gastrointestinal bleeding, secondary to iron deficiency anaemia [30]. Some authors found an association of GAVE with the presence of antibodies against polymerase III.

Motility disorders in the course of SSc often also occur in the intestines. This leads to increased intestinal transit, intestinal pseudo-obstruction in many cases, diverticulosis, bowel microperforation, bacterial contamination syndrome (small intestinal bacterial overgrowth), leading to diarrhoea, malabsorption syndromes, deficiency syndromes including vitamin B12 deficiency and ultimately malnutrition, cachexia and premature death [31].

Bowel involvement can cause chronic constipation.

Less than 10% of SSc patients have symptoms of primary biliary cirrhosis [32].

KIDNEYS

Renal involvement is found in approximately 40–80% of SSc patients.

The most common form of renal involvement is chronic kidney disease (60–80% of cases) otherwise known as the latent or oligosymptomatic/paucisymptomatic form of renal involvement. Chronic kidney disease is marked by a slow decline in glomerular filtration rate, which then leads to a gradual rise in serum creatinine levels until advanced renal failure develops [33].

The first clinical manifestation of renal involvement may be proteinuria, haematuria, or moderate hypertension, which can often be completely missed and unnoticed.

A special place is occupied by Scleroderma renal crisis (SRC) which is associated with vascular microangiopathy, hypertension and rampant acute renal failure.

Predisposing factors for SRC:

— early period of the disease (especially the first 4 years after diagnosis);
— male sex;
— black race;
— presence of serum anti-RNA polymerase III antibodies;
— previous treatment with glucocorticosteroids, cyclosporine or nonsteroidal anti-inflammatory drugs.

There are 2 types of scleroderma renal crisis.

Hypertensive SRC can be diagnosed when [34]:

• *De novo* hypertension was diagnosed:
— RR > 140/90 mm Hg,
— an increase in systolic blood pressure of 30 mm Hg,
— an increase in diastolic pressure of 20 mm Hg; and
• plus one of the following five symptoms:
— an increase of 50% in creatinine levels compared to the previous test or creatinine levels above 120% of the upper limit of the laboratory standard,
— proteinuria or haematuria detected by a strip test,
— thrombocytopenia < 100 G/L,
— haemolysis defined as anaemia unrelated to another cause and with the presence of the following: schistiocytes or other erythrocyte fragments in the smear,
— increase in reticulocytes.

Normotensive SRC is diagnosed when [34]:

• a 50% increase in creatinine levels compared to the previous test or creatinine levels above 120% of the upper limit of the laboratory standard;
• plus one of the following five symptoms:
— proteinuria or haematuria detected by a strip test,
— thrombocytopenia < 100 G/l,
— haemolysis defined as anaemia unrelated to another cause and with the presence of schistiocytes,
— increase in reticulocytes,
— renal biopsy with signs of microangiopathy typical of SRC.

The introduction of angiotensin-converting-enzyme inhibitors (ACE-i) into the therapy of SRC has significantly improved the prognosis of patients. However, a report published in Arthritis Research & Therapy by Bütikofer et al. [35] and the EUSTAR (European Scleroderma Trials and Research) group indicates that ACE-i adversely affect the risk of SRC and that

the use of ACE-i in patients with SSc and hypertension is an independent risk factor for this complication. Perhaps the use of drugs from another hypertensive drug class, namely angiotensin II receptor blockers, would be justified.

However, the most important thing is to closely observe and monitor SSc patients from a renal perspective to prevent the need for renal replacement therapy in these patients as much as possible.

CONCLUSIONS

Systemic sclerosis continues to be a major challenge for doctors in many specialties. The variety of clinical manifestations, the still unknown cause, the insidious onset, and course of this condition require thorough and reliable — often multidisciplinary — treatment. The management of systemic sclerosis is also a difficult task. Despite the emergence of new therapeutic methods, organ-specific therapy, which targets individual systems and organs involved in the disease process, still appears to be the only valid treatment .

CONFLICT OF INTEREST

None declared.

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