CREST Syndrome - a Limited Form of Systemic Scleroderma: a Case Report and Literature Review

Mirjana PARAVINA¹, Milenko STANOJEVIĆ¹, Ljiljana SPALEVIĆ¹,², Dragana LJUBISAVLJEVIĆ², Zorana ZLATANOVIĆ², Danijela POPOVIĆ²

¹Medical Faculty, University of Niš, Serbia
²Clinic of Skin and Venereal Diseases, Clinical Center of Niš, Serbia

¹Correspondence: Mirjana Paravina, E-mail: mirjanaparavina@gmail.com

Abstract

Systemic scleroderma (SSc) is a multisystem disease with microvascular abnormalities, autoimmune disorders, excessive collagen production and deposition, fibrosis of the skin and internal organs. According to the simplest, though incomplete classification, there are two forms of SSc: diffuse and limited (formerly acrosclerosis). CREST syndrome is a subtype of limited SSc, characterized by: calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. We present a patient with all the features of the CREST syndrome, which appeared at the age of 43 and lasted for 23 years. The patient presented with a gradual development of symptoms during the first ten years, from Raynaud’s phenomenon, skin sclerosis, calcinosis, telangiectasia, and esophageal dysmotility. The diagnosis was based on clinical findings and relevant diagnostic procedures. The article presents a literature review on the epidemiology, etiology, pathophysiology, clinical manifestations, various attempts at classification, diagnostic criteria, and therapeutic modalities.

When classifying systemic scleroderma into two main types — diffuse and limited, with CREST syndrome as a variant of the latter, it should be pointed out that both types represent clinical forms of systemic sclerosis, share similar visceral involvement, laboratory abnormalities and course which is variable, as was the case in our patient.

Key words

Scleroderma, Systemic; CREST Syndrome; Signs and Symptoms; Diagnosis

© 2015 The Serbian Association of Dermatovenereologists
classification of SSc (10), differentiating acral systemic scleroderma, or sclerodactyly and proximal systemic scleroderma; the single major criterion is scleroderma proximal to the digits, affecting the limbs, face, neck or trunk; or at least two minor criteria such as sclerodactyly or digital pitted scarring or bilateral basal pulmonary fibrosis. In 1996, the Committee of the American Academy of Dermatology proposed a comprehensive classification of cutaneous sclerosis in three large groups: A. primary cutaneous sclerosis, which includes diffuse systemic or limited systemic (CREST syndrome), localized or circumscribed without involvement of internal organs, part of the overlap syndrome (mixed and poorly differentiated connective tissue disease) and eosinophilic faciitis; B. secondary cutaneous sclerosis as a result of GVHD (graft versus host disease), use of medications, intoxication, infection; C. prodromal cutaneous sclerosis syndromes, primarily Raynaud’s phenomenon (11). Apart from diffuse and limited systemic cutaneous sclerosis, in 2001, LeRoy and Medsger described also ectopic calcinosis and telangiectasias and limited unclassified prescleroderma, the so-called pre-systemic scleroderma, the so-called pre-systemic scleroderma (12). They introduced new criteria, including nailfold capillary microscopic abnormalities and the presence of autoantibodies, in order to establish patients with early limited systemic sclerosis without skin involvement. It is also called SS without skin involvement, visceral sclerosis, or SS sine scleroderma (13, 14).

In 2004, Maricq and Walter selected the following criteria for the classification of systemic sclerosis (SS): 1. sclerodermatous skin involvement; 2. microvascular abnormalities specific to SSc: SD-type nailfold capillary changes and/or CREST-type capillary telangiectasia; 3. presence of anticentromere antibodies (ACA) (14). Based on these criteria they proposed the following classification:

I Diffuse sclerosis (all three criteria)
II Intermediate sclerosis (2 criteria)
III Digital sclerosis (one criterion)
IV Sclerosis without skin involvement (none of the criteria)
V Insufficiently differentiated connective tissue disease with sclerosis (one or none of the criteria)
VI CREST (one or none of the criteria).

In 2007, Walker et al. adapted the LeRoy and Medsgers classification which included the following types: limited systemic scleroderma, limited systemic scleroderma with cutaneous involvement, diffuse systemic scleroderma and diffuse fasciitis with eosinophilia (15).

Scleroderma spectrum disorders involve the existence of the following (16):
1. diffuse systemic sclerosis;
2. limited cutaneous systemic sclerosis with CREST syndrome as a variation;
3. systemic sclerosis sine scleroderma;
4. localized scleroderma with linear scleroderma;
5. mixed connective tissue disease with features of systemic sclerosis, polymyositis, and SLE.
6. overlap syndromes: systemic sclerosis plus polymyositis, rheumatoid arthritis, or SLE.
7. scleroderma mimics - amyloidosis, chronic graft-versus-host disease, diffuse fasciitis with eosinophilia, eosinophilia-myalgia syndrome, nephrogenic fibrosing dermopathy, paraneoplastic syndromes, sclerodema, scleromyxedema (papular mucinosis), toxic oil syndrome;
8. undifferentiated connective tissue disease: multiple nonspecific, serologic or clinical abnormalities that do not meet ACR (American College of Rheumatology) criteria for rheumatic disease.

We report a patient with limited systemic scleroderma - CREST syndrome.

Case Report

A female patient, 66 years of age, first noticed skin changes at the age of 43. They progressed during the following 10 – 15 years, but after that time, they mostly persisted unchanged, with occasional bacterial and fungal secondary infections. The disease lasted for 23 years, and resulted in fatal outcome at the age of 66. In the last eleven years, she was hospitalized several times.

The first symptoms appeared on the acral areas of hands which were cold, turning white, purple then red. At first, the attacks were cold induced, later they became more frequent, regardless of the temperature, involving the toes as well. In the following two years, these were the only symptoms of the disease, but later the fingers got pale, hard, with impaired mobility,
subsequently leading to inability to fully stretch them, which significantly affected activities of daily living. The nails became thin and fragile. The skin of the distal portions of the arms and legs became thinner and tight. The involvement of the face started five years after the appearance of first symptoms; facial skin also became tight, thin and hard, without wrinkles. The face became smaller, wrinkles were prominent around the mouth, whereas dry mouth caused difficulties when smiling, laughing, talking or chewing food. Then, firm yellowish nodules developed on the finger joints, as well as large solid nodules on the shoulders and thighs. At that time, the patient started experiencing difficulties swallowing, heartburn, and regurgitation after large meals. No other organ involvement was reported.

The patient reported no serious illnesses. There was no family history of a similar condition.

Physical examination
Upon skin examination, the skin was pale, yellowish in color, taut, smooth, and mask-like. The face got smaller, with radial furrows around the mouth, causing the skin to stretch so that the few residual teeth were visible due to gingival retraction. The beaked nose and deep-sunken eyes have contributed to a typical “bird-like” face (Figure 1). The fingers were semiflex, very sclerotic, cold (“Madonna fingers”), tapered at the ends, with shortened distal phalanges, and apparent shortening of thinned nail plates (Figure 1). The dorsal sides of hands presented with small calcifications over the joints, above which the skin was paper thin and pale yellowish in color. Blotchy hyperpigmentation and telangiectasias were also present. The skin of the lower legs and feet exhibited similar characteristics, with pronounced telangiectasias in the form of spots or dark red lacy lines, with cyanosis, hypo- and hyper-pigmentation, and scars, while the nail plates were thickened (Figure 2). The interdigital areas were presented with madidation and maceration, erythema, erosions and scaling due to secondary fungal infection. Both sides of the gluteal areas were affected by infiltrates with inflamed skin and fluctuation. There

Figure 1. The face is tightening; the skin is thin, with radial furrows around the mouth, mask-like and expressionless. The fingers are semiflex, very sclerotic, with shortened distal phalanges, and apparent shortening of thinned nail plates
are deposited in the gluteal soft tissues, presenting as grouped oval pinhead- or millet-sized shadows reaching the size of a "green walnut"; lime salts are also observed in other parts of the pelvis (Figure 4). Esophageal peristalsis: the esophagus is normally positioned, dilated, without peristalsis or visible wrinkles, funnel-shaped in the kardia region, with slow flow of barium suspension (Figure 5).

**Therapy**

The patient received systemic therapy: antibiotics (penicillin, gentamicin), corticosteroids, progesterone, vasodilators (pentoxifylline), griseofulvin, and multimvitamin preparations; corticosteroids and antimycotics were administered topically. Apart from successful management of the secondary infection, some improvement was achieved by progesterone: the skin was softer, finger mobility was slightly better, and the patient subjectively felt better. However, dissolution of calcifications was not achieved by the applied therapy.
Discussion and Literature Review

Systemic sclerosis (SS) is a rare disease that is more common among women than men, with the peak age of onset between 20 and 50 years (17). The true incidence and prevalence of the disease are unknown, mostly due to a small number of published epidemiological studies, a large variability in the clinical manifestations and severity of the disease, the difficulty in applying classification criteria, and the variability in the design and methods used in epidemiological studies (18). A group of French authors analyzed 32 articles published from 1969 to 2006 in which the prevalence of SSc (systemic sclerosis with sclerosis of the skin) (SSc) ranged from 7/million to 489/million and its incidence from 0.6/million/y to 122/million/y (18). The prevalence is higher in the US (276 cases per million adults) and Australia (233 cases per million) than in Japan and Europe (France, 158 per million, and England 88 per million). Higher prevalence was established in Afro Americans (315 cases per million) than in Caucasians (224.7 cases per million) (19). According to various studies, the female to male ratio ranges from 1.1:1 (20) to 14:1 (21). Earlier onset of the disease is found in women in regard to men (average age for men 58.9 ± 13.5 years, and 49.2 ± 15.7 years for women (22). SS is rare in children (23).

Systemic scleroderma (SSc) is a SS affecting the skin and a multisystem connective tissue disease of unknown etiology, but it is certainly associated with genetic factors, immune system alterations, and environmental factors (15, 18, 24). Its pathogenesis involves vascular abnormalities resulting in tissue hypoxia, immune responses manifesting with altered T- and B-lymphocyte functions and production of autoantibodies, through fibroblast dysfunction and excessive collagen synthesis (25, 26, 27). A wide variety of hypotheses have been offered to explain the pathogenesis of SSc (25).

Figure 4. Pelvis x-ray revealing oval pinhead- or millet-sized, grouped shadows in the gluteal soft tissues
The immune hypothesis and autoimmune events in the pathogenesis of the SSc is supported by: elevated serum interleukin-2 levels, activated lymphocytes in the biopsy specimens, activated monocytes in the peripheral blood, reduced number of CD8+ T lymphocytes, impaired function of NK (natural killer) cells, presence of various autoantibodies and immune complexes (25).

Some environmental factors may play a role in triggering SSc in persons with genetic predisposition, such as physical trauma (long-term exposure to vibration, burns) (11), viral infections (cytomegalovirus, parvovirus B19, herpes virus) or helicobacter pylori, toxic substances (vinyl chloride, some pesticides, benzene derivatives, silica, trichloroethylene, organic solvents, epoxy resins), and drugs (cocaine, appetite suppressants, penicillamine,

Although familial cases of SSc are rare, a family case history is an important factor in the development of the disease (28). Genetic factors clearly influence disease susceptibility as a complex that includes a number of genes and chromosomal loci (24). The HLA (human leukocyte antigen) genes have been implicated in the susceptibility to SSc (29). Multiple genetic patterns in SSc, and various HLA alleles are associated with different clinical and serological aspects of this disease (30).

The immune hypothesis of SSc pathogenesis emphasizes the role of T cell-derived cytokines implicated in the damage of the blood vessels and indirectly tissue hypoxia; they also directly stimulate fibroblasts to increased collagen synthesis. T helper lymphocytes impair humoral immunity and increase in titer of antinuclear antibodies. The
vitamin K, bleomycin, isoniazid) (11, 31, 32). Relations between systemic sclerosis and occupational exposure to certain chemicals as triggers of systemic scleroderma have been investigated, for example in construction workers and miners who work with explosives, but later studies showed this association to be unreliable (33). There are authors who believe that occupational exposure to organic solvents is not significantly associated with systemic scleroderma, and one should be cautious in interpreting the impact of organic solvents and certain chemicals on the development of scleroderma in textile workers (34).

According to the vascular hypothesis of the SS pathogenesis, primary changes affect the blood vessels (intimal thickening and vessel lumen occlusion). Endothelial cells are among the first targets, or primary dysfunctional cells in this disease (35). Precapillary sphincter dilation causes microvascular hypertension, swelling, telangiectasia, and later arteriolar hyperplasia and fibrosis. It is possible that blood vessel insufficiency causes tissue injury, whereas fibrosis is a part of the repairation process. Excessive collagen production results in fibrosis of the skin and internal organs; collagen (types I, III, IV, and VII), fibronectin, glycosaminoglycans, and proteoglycans are deposited in the interstitium and in the intima of small arteries (36). Collagen deposition may be caused by increase in the number of fibroblasts which produce collagen, or increased collagen production in fibroblasts, but also by reduced collagen degradation.

The acronym CREST stands for calcinosis, Raynaud’s phenomenon (RPh), esophageal dysmotility, sclerodactyly, telangiectasia syndrome, and dates back to the twentieth century: in 1911, Thibierge and Weissenbach described a patient with skin calcinosis, RPh, sclerodactyly and telangiectasia, and named it CRST syndrome (37). In 1964, Winterbauer registered esophageal dysmotility in 4 of his 8 patients with CRST syndrome (38), and in 1973, Frayha et al. proposed the acronym CREST, due to common occurrence of esophageal dysmotility (39). Later, various combinations of these clinical manifestations have been described, including REST syndrome (without calcinosis), CRest, “Pure” CREST (in patients with two or more symptoms of CREST, but not enough criteria for limited or diffuse systemic sclerosis), “Plus” CREST (association with other forms of systemic scleroderma - limited or diffuse, or with other autoimmune diseases) (40). Our patient was diagnosed with CREST syndrome, fulfilling all criteria. Due to common absence of some manifestations, some authors believe it is more correct to speak about limited cutaneous scleroderma, and that presence of two of five manifestations is sufficient (3), however, this is unlikely to be a separate syndrome distinct from systemic sclerosis, but only a subgroup of systemic sclerosis (41).

Calcinosis is one of the typical manifestations of CREST syndrome, but it may occur in all types of scleroderma. Calcinosis occurs in about 25% of patients with limited SSc and it can be associated with problems of poor peripheral circulation, causing local skin irritation, inflammation, ulceration and encouraging secondary infection (42). Calcinosis generally results from dystrophic calcification associated with massive collagen degeneration (43). Cutaneous deposition of calcium salts in the skin occurs in a variety of clinical settings, beginning as a calcium phosphate nidus and progressing to hydroxyapatite crystal formation within a collagen matrix (43). Dystrophic calcification is due to accumulation of calcium apatite crystals, with normal levels of serum calcium, phosphorus, and alkaline phosphatase (44). Calcium deposits develop in the skin, as subcutaneous nodules or massive nodes, mainly in the elbows, knees, fingers and toes, but also in other body areas (45). Sometimes they are visible, sometimes just palpable. The overlying skin is thin and often painful. The lumps may break through the skin and leak a chalky white liquid. Secondary infections and inflammations are not uncommon (26). Our patient presented with multiple calcifications of various localization and size, and at one point she needed surgical intervention.

Raynaud’s phenomenon (RPh) causes numbness, pain and color changes in fingers in a large number of patients with limited SSc (46). It was first described by Maurice Raynaud in 1862 (47). It is usually the first and often the only symptom of scleroderma for many years, hence its central role in diagnosis of SSc (45). It is usually triggered by exposure to cold or emotional stress; due to spasm of small blood vessels (capillaries) one or more fingers suddenly turn white, become cold and insensitive (48). After a few minutes or longer, lack of oxygen in the blood causes cyanosis and pain in the fingers, but when the circulation gets normal, hyperemia occurs and the skin gets red (49). Between
episodes the patient is symptom free (26). Secondary RPh is typical for collagen and vascular diseases; it is usually asymmetric and may be accompanied by ulcerations or necrosis. Primary RPh affects younger individuals, after stressful events or exposure to cold; changes are symmetrical without ulcerations and necrosis (3).

At the age of 43, our patients presented with RPh symptoms, initially after exposure to cold, and later regardless of environmental factors; for two years it was the only manifestation of the disease.

Esophageal dysmotility: Although patients with SSc present with changes in the entire gastrointestinal tract, esophageal involvement is most common (26). The majority of patients with CREST syndrome demonstrate hypomotility. The esophageal epithelium may show a cobblestone appearance due to pearly white plaques; apart from subepithelium, fibrosis may also affect regions with muscle atrophy (41). Apart from esophageal aperistalsis, spasms and esophageal stricture have rarely been reported. Esophageal manometry and radionuclide transit test are better than radiography in the detection of motor abnormalities (41).

Esophageal dysmotility is usually found in the lower two-thirds of the esophagus and the lower esophageal sphincter, due to smooth muscle atrophy and fibrosis of the lamina propria and submucosa, atrophy and mucosal erosion and disruption of the capillary network (1). Patients often state they must drink liquids to swallow solid food (50). Esophageal reflux is common (16), as well as nausea, vomiting, weight loss, diarrhea, constipation and bleeding (45, 49). It has been pointed that symptoms of esophageal reflux are twice as common as dysphagia (41).

After five years since the beginning of the disease, our patient presented with difficulties in swallowing, heartburn, and regurgitation with large meals.

Sclerodactyly is the most easily recognizable manifestation, but it is not prominent in all patients (50). It is thickening which generally only involves the skin of the fingers (and toes) distal to the metacarpophalangeal joints in CREST syndrome. Sclerodactyly evolves through three phases: the edematous phase, indurative phase, and atrophic phase (26): the edematous phase begins with finger swelling, morning stiffness, and arthralgias; in the second phase the skin becomes thickened, shiny, without wrinkles, erythematous, and itchy; in the last, atrophic phase, the skin becomes fragile and lax, although it looks thicker due to thight connections with the structures underneath (1). The fingertips are pointed, fixed in an acutely flexed position, with ulcerations and calcifications. The distal phalanges are shortened or missing, hands are stiffened into a claw and immovable (48). The nails are dystrophic, dry, striated, deformed. Skin distal to the elbows and knees, but also of the neck and face may be involved.

Three years after the appearance of RPh, our patient presented with skin changes on her fingers: first edema, then thickening, thinning, accompanied by reduced mobility and fixed flexion. There were also nail changes. Changes on the face and calcifications were registered 5 years after the onset of the disease.

Telangiectasias may occur in all types of SSc. They affect the face and extremities due to dilation of blood vessels on the skin surface, but also on the mucous membranes (lips, digestive tract) (26). The number and locations of telangiectasias increase over time (50). Our patient had numerous telangiectasias and scars on the shins and dorsum of the feet.

Other symptoms of CREST syndrome include fatigue, weakness, breathing difficulties, dizziness, ulcerations on the fingers and toes, poor wound healing, dry mouth and eyes, problems with the teeth.

Although the majority of patients may be classified into diffuse or limited SSc, there is a possibility of overlapping clinical symptoms, so all patients are at risk for complications of SSc (51).

Pulmonary arterial hypertension is a significant cause of mortality in SSc (52). The prevalence of pulmonary arterial hypertension in diffuse SSc ranges from 4.9% to 26.7% (53). However, pulmonary arterial hypertension may be a complication of limited SSc as well (54, 55).

Scleroderma renal crisis is a rare but serious complication of SSc (56). It is defined as severe hypertension associated with rapid increase in serum creatinine, with or without microangiopathic hemolytic anemia (57). It occurs in about 20% of patients with diffuse SSc, but it also affects patients with limited SSc and CREST syndrome (58, 59, 60). Regular renal function monitoring is recommended for all patients with SSc. Corticosteroids, especially high doses, represent a risk for scleroderma renal crisis (61).

Primary biliary cirrhosis (PBC) may also be accompanied by CREST syndrome. The association
of these two diseases is explained by a common autoimmune mechanism, and it is considered a distinct entity (PBC-CREST). Along with keratoconjunctivitis sicca, it is known as Raynaud’s syndrome. According to Tojo and associates (62), patients with PBC-CREST have milder symptoms than patients with PBC or CREST alone, but have a larger number of esophageal varices. High titers of anti-centromere antibodies (ACA), low titers of anti-mitochondrial antibodies, high prevalence of HLA-DR9 and better prognosis are registered in patients with PBC-CREST. This association is well known in women, but it may also occur in men (63).

Using non-invasive cardiovascular magnetic resonance (CMR) imaging (64), coronary artery abnormalities and myocardial fibrosis can be registered, and all patients with SSc present with multiple fibrotic areas (65). The pathogenesis of the fibrotic lesions in SSc is still unclear. However, a spasm of small coronary arteries (myocardial Raynaud’s phenomenon) has been suggested as a possible mechanism (65). Mavrogeni et al. (66), used CMR to evaluate 5 patients with CREST syndrome and 5 patients with SSc. All patients with CREST syndrome presented with coronary artery ectasia, whereas patients with SSc were without cardiac symptoms with normal coronary artery findings, but patchy fibrosis was identified in all of them (66).

Anemia has also been associated with CREST syndrome (67) as a result of jejunal telangiectasias, with normal colposcopic findings and esophagitis.

Lauritano et al. (68) observed tongue rigidity and some speckled red alternating with white spots on the hard palate and in the vestibule in patients with Sjögren’s syndrome and CREST.

CREST syndrome is rarely associated with other malignancies (69). It has been suggested that patients with scleroderma and Barrett’s metaplasia are at increased risk of complications, such as strictures or adenocarcinoma, cases of CREST syndrome and lung adenocarcinoma, esophageal carcinoma, and adenocarcinoma of the third portion of the duodenum (41, 69).

Hachulla and Launay (70) reviewed the literature concerning the diagnosis and classification of SSc, describing characteristics of certain forms of the disease. In diffuse cutaneous form of SSc, disease progression is very fast, with a high incidence of renal, cardiac and pulmonary alterations (71).

These characteristics also include: RPh episodes with fast skin changes, changes on the trunk and acral parts of the body, presence of tendon friction rubs, early and significant appearance of interstitial lung disease, chronic renal failure with oliguria, diffuse gastrointestinal diseases, with involvement of myocardium, genitourinary and musculoskeletal system, absence of ACA, dilatation of capillaries and nailfold capillary destruction, autoantibodies against Topoisomerase I (Scl 70) (in 30% of patients) (10, 16). The limited cutaneous SSc is characterized by slow progression, and less frequent and later spread on the internal organs. RPh is recorded in the course of several years, skin sclerosis affects the hands, face, legs and forearms (acral parts); there is a significantly lower incidence of pulmonary hypertension, with or without interstitial lung disease, trigeminal neuralgia, calcification and skin telangiectasia, often with ACA (anticentromere antibody that reacts with the kinetocore of metaphase chromosomes) in 40 - 70% (41), dilated nailfold capillaries (10).

Systemic sclerosis sine scleroderma (ssSSc) is a rare disorder in which patients develop vascular and fibrotic damage to internal organs, in the absence of cutaneous sclerosis (72). Brazilian authors studied 947 consecutive patients with SSc and 8.3% were classified as ssSSc (73). In this series, patients with ssSSc had a relatively mild type of disease with good prognosis. The disease was characterized by (13): RPh with a peripheral vascular equivalent (digital pitting scars, digital tip ulcers, digital tip gangrene and abnormal nailfold capillaries), positive antinuclear antibodies (ANA), one visceral organ involvement typical of SSc (any one of the following: distal esophageal hypomotility, small bowel hypomotility, pulmonary interstitial fibrosis, pulmonary hypertension, cardiac involvement typical of scleroderma or renal failure consistent with scleroderma renal crisis) and absence of another defined connective tissue or other disease as a cause of signs and symptoms cited above.

Scleroderma overlap syndromes mostly include simultaneous occurrence of scleroderma and some autoimmune systemic diseases (polymyositis, systemic lupus erythematosus or rheumatoid arthritis). If only RPh, ulcers, digital pitting ulcers, and ANA are present, with no other signs of systemic disease, it is presystemic scleroderma (1), corresponding with prodromal cutaneous sclerosis syndrome.
Rare cases of nodular and keloidal scleroderma have also been described. There are two categories: 1) systemic scleroderma accompanied by generalized distribution of ivory-colored subcutaneous nodules 3-20 mm in diameter, whose histology shows fibromatous changes or fibrinoid necrosis, and 2) localized scleroderma, subcutaneous morphea/deep morphea/morphea profundus, with localized or generalized nodules; the skin is pigmented or hypopigmented, while most morphea nodules are said to be non-progressive (41). Localized scleroderma is characterized by extensive deposition of collagen with a thickening of the dermis and/or subcutaneous tissue. Unlike systemic sclerosis, it presents without scleractactyly, RPh, nail changes, telangiectasia and progressive involvement of internal organs (41).

Speaking of patients with SSc, the most common subsets are limited cutaneous (approximately 60% of patients with systemic sclerosis) and diffuse cutaneous (approximately 35% of patients with systemic sclerosis), whereas systemic sclerosis without scleroderma affects about 5% (16). Approximately 15% of patients have pulmonary hypertension, and 10% have overlap syndromes.

**The diagnosis of systemic sclerosis** is based on the following (11, 41):

A. Clinical findings: 1) Medical history (on the overall health status, development of the disease and symptoms, exposure to possible precipitating factors, symptoms involving the lungs, heart, gastrointestinal tract, kidneys, muscles, etc.). 2) Clinical examination of the skin and other organs, and diagnostic criteria;

B. Diagnostic tests: Erythrocyte sedimentation rate, blood count, biochemical analyses; Skin biopsy; X-ray of the lungs, heart and esophagus; CT scan of the bones (in patients with calcinosis CT should be done when radiography findings are normal); Esophageal manometry and radionuclide transit are better than radiography for showing motor abnormalities; plethysmography, laser Doppler flowmetry, thermography, finger systolic blood pressure are used in the RPh (26); Cardiovascular magnetic resonance imaging is used to detect changes in the coronary arteries and the heart muscle, but major differences between limited and diffuse SSc are not probable (74).

The diagnosis of RPh is made using: plethysmography, laser Doppler flowmetry, thermography, finger systolic blood pressure (26). Serological tests: antinuclear antibodies (ANA) (90% - 95% in limited cutaneous and diffuse cutaneous SSc) (75). Other tests are used depending on the affected organ: pulmonary function tests, chest radiography, electrocardiogram, gastrointestinal motility testing, renal function tests, etc.

C. Diagnostic criteria of the American College of Rheumatology (ACR) (9). The patient should fulfill a major criterion or two of the three minor criteria:

I Major criteria - Scleroderma proximal to the digits, affecting limbs, face, neck or trunk - this is a single major criterion.

II Minor criteria;
(a) sclerodactyly
(b) digital pitted scarring
(c) bilateral basal pulmonary fibrosis.

Nadashkevich et al. (76) have proposed nine criteria - ABCDECREST: A. autoantibodies to: centromere proteins, Scl-70 (TOPO I), or anti-fibrillarin; B. bibasilar pulmonary fibrosis; C. contractures of the digital joints or prayer sign; 4. D. dermal thickening proximal to the wrists; 5. C. skin calcinosis; 6. RPh - Raynaud's phenomenon; 7. E. - esophageal distal hypomotility or reflux-esophagitis; 8. S. - sclerodactyly or non-pitting digital edema; 9. T. - telangiectasias. The classification of definite SSc requires at least three of the above criteria. Although presence of topoisomerase 1 (Scl-70) is extremely rare in localized scleroderma, autoantibodies to topoisomerase 11 were found in 70% of patients with localized scleroderma, and 85% of patients with generalized morphea (41).

Classification criteria for systemic sclerosis, published by the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative (77) in 2013, include 8 criteria validated by a number of points, so that the definite diagnosis of SSc is set if the total score is 9 or more. These are: 1) skin thickening of fingers of both hands extending proximally to the metacarphophalangeal joints (sufficient criterion - 9 points); 2) finger tip lesions, edema - 2 points, sclerodactyly - 4 points; 3) finger lesions, ulcerations - 2 points; finger tip-pitting scars - 3 points; 4) telangiectasias - 2 points; 5) abnormal nailfold capillaries - 2 points; 6) lung involvement, pulmonary arterial hypertension - 2 points; interstitial lung disease - 2 points; 7) RPh - 3 points; 8) scleroderma related antibodies - 3 points.
In recent years a number of authors (78 - 82) is working on the revision of the classification criteria, including a broad range of clinical and laboratory elements that characterize SSc, which should contribute more accurate diagnosis, therapy and prevention of complications of the disease. Nailfold capillary microscopy (NCM) is a method used to assess the degree of capillary dilation (83), being very important for early diagnosis of SSc. NCM has significantly improved the identification of clinical differences (84), and that is why diagnostic sensitivity of ACR criteria may be markedly improved by addition of simple clinical variables, including NCM abnormalities and ACA positivity, as novel minor criteria (83). Capillary patterns may correlate with visceral involvement and capillaroscopy thus has the potential as a screening tool to enable early diagnosis of organ involvement in systemic sclerosis, as well as early therapy and prevention of disease progression (85). This method allows: early diagnosis of systemic sclerosis without skin involvement, differentiation of primary RPh from secondary RPh and follow up of disease progression (86). Today, videocapillaroscopy is most widely used (87). When comparing NCM and dermoscopy, most nailfold capillary images can be classified and assessed with higher accuracy (88).

Serological tests are of great importance in the diagnosis and differential diagnosis, especially related to the presence of antinuclear antibodies (ANA), which are the expression of autoimmune response (35), and clinically are associated with pulmonary and arterial hypertension, and interstitial lung disease; ANA may be present in healthy individuals as well, but in low percentage (89). Anticentromere antibodies (ACA) are found in 40 to 70% of patients with limited cutaneous sclerosis and are associated with calcinosis, RPh, esophageal dysmotility, sclerodactyly, telangiectasia, and pulmonary arterial hypertension; they are found only in 2 to 5% of patients with diffuse scleroderma, when they are associated with digital ulceration or digital loss. ACA findings indicate capillary involvement (90). Anti-topoisomerase I (anti-Scl-70) autoantibodies are found in 20 to 40% of patients with diffuse cutaneous sclerosis, and only 6% with limited cutaneous SSc; they are associated with rapid progression of skin thickening, scleroderma, renal crisis, pulmonary fibrosis, joint, muscle and heart involvement, hypertension and proteinuria (91). Anti-fibrillin-1 antibodies (UI-RNP) indicate a serious involvement of skin and systemic organs with high mortality, whereas antinucleolar antibodies indicate a limited form of the disease; however, they can be detected in patients with pulmonary hypertension and pulmonary fibrosis (75). Anti-RNA Polymerase III (Pol 3) antibodies are registered in 10 - 20% of patients with SSc, pointing to a serious disease with scleroderma, renal crisis and association with malignancy (91).

There is a registered association between SSc and various HLA alleles (92). Scleroderma is associated with HLA-DQA1* 0501 and DQB1* 0301 allele in all ethnic groups, DRB1* 1104 in Caucasians and Hispanics, and DRB1* 0804 in African Americans (93). HLA-DRB1 alleles are associated with limited scleroderma (29), and B* 62, DRB1* 11 and DRB1* 07 with diffuse scleroderma (1, 94). Pulmonary fibrosis is associated with HLAB* 62 and HLA Cw* 0602, and pulmonary hypertension with HLAB* 13 and HLAB* 65 (29). There is a correlation between the connective-tissue growth factor (CTGF), and systemic sclerosis, particularly in patients with anti-Scl-70 antibodies and pulmonary fibrosis (95). The presence of certain HLA alleles correlates with the presence of autoantibodies specific for systemic scleroderma (93, 96).

**Differential diagnosis** includes (16, 41): RPh of occupational origin, vibration-induced injuries, other connective tissue diseases or mixed connective tissue diseases (eg, rheumatoid arthritis or systemic lupus erythematosus), undifferentiated connective tissue disease, amyloidosis, paraneoplastic syndrome, and pseudoscleroderma (congenital, metabolic, toxic, chronic graft-versus-host disease).

Despite numerous new findings, there is still no therapeutic algorithm that can significantly change the natural course of the disease. Symptomatic treatment is of great importance (35).

**The therapy** of SSc depends on the segment in the pathogenesis of the disease which is being treated, e.g. changes in the vascular system, increased collagen synthesis, or modified immune reactivity (1). Vasoactive treatment includes: prostacyclin, low molecular weight dextran, stanozolol, nifedipine, captopril, ketanserin and plasmapheresis. Collagen production is affected by: D-penicillamine, pentoxifylline, coagulation factor XIII, cyclofenil,
In some cases, clinical improvement in patients with SSc is obtained by UVA-1 phototherapy (98).

Meta-analysis was conducted to determine the efficacy of calcium channel blockers for RPh, pointing to a moderate reduction in the frequency and severity of ischemic attacks (99). The following blockers were evaluated: nifedipine, nicardipine, nisoldipine, diltiazem; nifedipine was indicated for RPh, since it significantly reduced the frequency and severity of ischemic attacks with highest therapeutic efficacy (100). Type V phosphodiesterase inhibitor, sildenafil, stimulates accumulation of cyclic guanosine monophosphate, decreasing intracellular calcium concentrations, inducing relaxation of the vascular smooth muscle and consequent dilation (101, 102). Several-week use of sildenafil causes significant reduction in the frequency and severity of RPh (102).

A synthetic phosphodiesterase III inhibitor, cilostazol increases conduit vessel diameter in patients with primary and secondary RPh, with a favorable impact on conduit vessel responsiveness to cold in patients with primary RPh without affecting microvascular flow or symptoms (103). Selective alpha-adrenergic receptor blocker acts in the recovery from cold-induced vasospasm in scleroderma patients (104). If topical glyceryl trinitrate is used in the treatment of primary RPh or limited SSc, it may cause endothelium-dependent vasodilator effect (105).

The mechanism of calcinosis formation is not entirely understood, and no effective treatment is available (106). However, low doses of warfarin may be effective in some patients with early and moderate SSc. Minocycline may be effective in the control of calcinosis in systemic sclerosis. The mechanism of action may be mainly through inhibition of matrix metalloproteinases and anti-inflammatory effects (42). Physical therapy of calcinosis includes: extracorporeal shock wave lithotripsy (107), carbon dioxide laser (108), and erbium laser (109). Treatment of finger calcinosis has a wide range of possibilities depending on the extent of calcifications and the involvement of deep structures. From a surgical point of view, simple removal is adequate in minor outpatient cases, whereas radical debridement is required in the major and more painful cases (44). Laser surgery may reduce telangiectasias, and amputation is sometimes necessary in gangrene.

In some cases, clinical improvement in patients with SSc is obtained by UVA-1 phototherapy (98).

Meta-analysis was conducted to determine the efficacy of calcium channel blockers for RPh, pointing to a moderate reduction in the frequency and severity of ischemic attacks (99). The following blockers were evaluated: nifedipine, nicardipine, nisoldipine, diltiazem; nifedipine was indicated for RPh, since it significantly reduced the frequency and severity of ischemic attacks with highest therapeutic efficacy (100). Type V phosphodiesterase inhibitor, sildenafil, stimulates accumulation of cyclic guanosine monophosphate, decreasing intracellular calcium concentrations, inducing relaxation of the vascular smooth muscle and consequent dilation (101, 102). Several-week use of sildenafil causes significant reduction in the frequency and severity of RPh (102).

A synthetic phosphodiesterase III inhibitor, cilostazol increases conduit vessel diameter in patients with primary and secondary RPh, with a favorable impact on conduit vessel responsiveness to cold in patients with primary RPh without affecting microvascular flow or symptoms (103). Selective alpha-adrenergic receptor blocker acts in the recovery from cold-induced vasospasm in scleroderma patients (104). If topical glyceryl trinitrate is used in the treatment of primary RPh or limited SSc, it may cause endothelium-dependent vasodilator effect (105).

The mechanism of calcinosis formation is not entirely understood, and no effective treatment is available (106). However, low doses of warfarin may be effective in some patients with early and moderate SSc. Minocycline may be effective in the control of calcinosis in systemic sclerosis. The mechanism of action may be mainly through inhibition of matrix metalloproteinases and anti-inflammatory effects (42). Physical therapy of calcinosis includes: extracorporeal shock wave lithotripsy (107), carbon dioxide laser (108), and erbium laser (109). Treatment of finger calcinosis has a wide range of possibilities depending on the extent of calcifications and the involvement of deep structures. From a surgical point of view, simple removal is adequate in minor outpatient cases, whereas radical debridement is required in the major and more painful cases (44). Laser surgery may reduce telangiectasias, and amputation is sometimes necessary in gangrene.
• broad-spectrum topical antibiotics;
• nitroglycerin ointment for ischemic ulcers;
• topical antipruritics;
• emollients.

Other forms of therapy (31, 32):
• patient education on the characteristics of the disease and awareness of urgent problems;
• physiotherapy to promote joint mobility and muscle strength;
• exercises to maintain range of motion (mouth, face and hand stretches);
• avoid tobacco and maintain healthy weight;
• nutritional advice, and supplements if needed;
• for Raynaud’s phenomenon: avoid cold and trauma, use warm clothing or heated clothing; For an attack - warm the body, hands and feet, use gentle arm movements or gentle massage to help restore circulation;
• occupational therapists - for adaptations to assist in daily living;
• camouflage products – cosmetics.

Skin protection: Avoid harsh soaps and detergents; reduce bathing frequency (bathe just once a day or every other day, using warm rather than hot water); apply sunscreen and increase moisture levels in your home by using a humidifier;
• practice good oral hygiene.

The prognosis and course of the disease indicate that although spontaneous remission is possible, SSc is essentially a chronic disease with progressive course with possible crises due to organ involvement. The patient should be informed about the objective circumstances in terms of clinical manifestations and treatment options, with high commitment of the entire team of doctors and psychotherapy.

Conclusion
When classifying systemic scleroderma into two groups - diffuse and limited, with CREST syndrome as a variant of the latter, it should be considered that both types represent clinical variants of systemic sclerosis, share similar visceral involvement, laboratory abnormalities and the course which is not invariable, as shown in our patient. We reported a case of a patient with typical features of limited SSc, and all the symptoms of CREST syndrome, in whom the disease lasted for 23 years; therapeutic modalities provided only temporary improvement, eventually resulting in a fatal outcome.

Abbreviations
SSc – systemic scleroderma
CREST – Calcinosis, Raynaud’s phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasia
SS – systemic sclerosis
ARA - American Rheumatism Association
GVHD - graft versus host disease
ACR - American College of Rheumatology
HLA - human leukocyte antigen
IL - interleukin
NK - natural killer
RPh – Raynaud’s phenomenon
PBC - primary biliary cirrhosis
ACA – anti centromere antibodies
Scl 70 - topoisomerase 1
ssSSc - SSc sine scleroderma
ANA - antinuclear antibodies
NCM - nailfold capillary microscopy
CTGF - connec tive-tissue growth factor
TNF - tumor necrosis factor

References

© 2015 The Serbian Association of Dermatovenereologists


Larch M. What’s new in Scleroderma. [cited 2015 Oct 1]. Available from: http://static1.squarespace.com/static/52b05f9e94a0b0f06a2504a7/52decbe0e4b0f1b2ead9eb0ba/13933268009/Whats+new+in+Sclerodermia+8th+Jan+2014.pdf.


CREST sindrom - ograničena varijanta sistemske skleroderme: prikaz slučaja i pregled literature

Sažetak

Uvod. Sistemska skleroderma (SSc) je multisistemska bolest sa mikrovaskularnim abnormanostima, autoimunskim poremećajima, pojačanom produkcijom i depozicijom kolagen i fibrozom kože i visceralnih organa. U osnovi radi se o sistemskoj sklerozi (SS) u kojoj skleroza zahvata i kožu. Prema najjednostavnijoj, mada ne i kompletnoj klasifikaciji, registruju se dve forme SSc: difuzna SSc i limitirana (raniji naziv akralna) SSc. Podtip limitirane SSc je CREST sindrom, čije su karakteristike: kalcinoza, Rejnoov fenomen (RF), eozafalno dismotilitet, sklerodaktijla i teleangiektazije.

Prikaz slučaja. Prikazana je bolesnica sa tipičnom kliničkom slikom limitirane SSc i svim elementima CREST sindroma, kod koje je bolest počela u njoj 43. godini i trajala 23 godine, sa postepenim razvojem bolesti u prvih desetak godina, počev od Rejnoovog fenomena, skleroze kože, kalcifi kacija, telangiektazija do dismotiliteta ezofagusa. Primjenjvana terapija je dovodila do privremenih poboljšanja, da bi konačno rezultirala smrtnim ishodom.

Dijagnoza je postavljena na osnovu kliničke slike i relevantnih dijagnostičkih procedura.


Kriterijumi za klasifikaciju sistemske skleroze koje je 2013. objavio Američki koledž za reumatologiju i Zajednička inicijativa Evropske lige protiv reumatizma (American College of Rheumatology (ACR)/ European League Against Rheumatism Collaborative Initiative), obuhvata 8 kriterijuma koji su vrednovani određenim brojem poena, tako da se definitivna dijagnoza SSc može postaviti ako je ukupan skor 9 ili više. To su: 1. zadebljanje prstiju obeju ruku proksimalno od metakarpofalangealnih zglobova (dovoljan kriterijum – 9 bodova); 2. zadebljanje prstiju, otok − 2 poena, sklerodktilija − 4 poena; 3 lezije prstiju, ulceracije − 2 poena, ispod ravni kože − 3 poena; 4. telangiektazije − 2 poena; 5. abnormalni kapilari nokatnog zaslona − 2 poena; 6. zahvaćenost pluća: pulmonalna arterijska hipertenzija − 2 poena, intersticijalna plućna bolest − 2 poena; 7. RF − 3 poena; 8. autoantitela tipična za sklerodermu (ACA anticientromerna, ili Scl-70 antitopomeraza 1 (TOPO I), ili anti-fibrilarin) − 3 poena.

U novije vreme veliki broj autora radi na reviziji klasifikacije I kriterijuma uvodeći širok dijapazon elemenata koji su klinički i laboratorijski karakteristični za SSc, što će svakako doprineti preciznijoj dijagnostici, terapiji i prevenciji komplikacija bolesti. Kapilarna mikroskopija zaslona nokatne ploče (engl. nailfold capillary microscopy - NCM) je metoda kojom se određuje stepen kapilarnih dilatacija, što je vrlo važno za ranu dijagnozu SSc. Kako kapilarne promene mogu da koreliraju sa visceralnim zahvatamjem, kapilaroskopija omogućava ranu dijagnozu organskih promena, što ima za rezultat rani početak terapije i prevenciju progresije i oštećenja organsa. Ovom metodom se omogućava rana dijagnostika sistemske skleroze bez zahvatanja kože, kao i razlikovanje primarnog od sekundarnog...
RF i registrovanje progresije bolesti. Danas je najviše u upotrebi video-kapilaroskop. Ukoliko NCM poredimo sa dermoskopijom, snimci dobijeni pomoću NCM se mogu klasifikovati i mogu se ozbiljnije procenjivati.

I pored brojnih novih saznanja, još uvek ne postoji terapijski algoritam koji može bitno promeniti prirodni tok bolesti. Od izuzetnog značaja je simptomatsko lečenje pacijenata. Lečenje SSc se planira zavisno od segmenta u patogenezi bolesti na koji se želi delovati, npr. na promene u vaskularnom sistemu, ili na povećanu sintezu kolagena ili izmenjenu imunsku reaktivnost. Za vazoaktivno lečenje primenjuju se: prostaciklin, niskomolekulski dekstran, stanozolol, nifedipin, kaptopril, ketaserin i plazmafereza. Na produkciju kolagena deluju: D-penicilamin, pentoksifilin, faktor koagulacije XIII, ciklofenil, kolhicin, griseofulvin, 13-cis retinoična kiselina. Za imunsku terapiju koriste se: prednizon, ciklofosfamid, azatioprin, ciklosporin. Hinhklif (Hinchcliff) i Varga su dali pregled lečenja organ-specifičnih komplikacija kod SSc:

- Rejnoov fenomen − alfa adrenergični blokatori, blokatori angiotenzin II receptor, dugodelujući (long-acting) blokatori kalcijumovih kanala (dihidropiridini), pentoksifilin (rental), blokade stelatnih gangliona, digitalna simpaktetomija;
- fibroza kože − imunomodulatori lekovi (d-penicilamin, mikofenolat mofetil, ciklofosfamid; gastro-ezofagealni refl uks – antacidii, H2 antihistaminici, inhibitori protonskih pumpe; intestinalni dismotilitet ili bakterijska infekcija − antibiotici, korekcija nutricione deficijencije, promotilentni agensi;
- pulmonalna fibroza ili alovitis – imunomodulatori, inicijalna terapija sa oralnim ili intravenoznim ciklofosfamidom, terapija održavanja – azatioprin;
- pulmonalna arterijska hipertenzija – diuretici, inhibitori endotelin-1 receptora (bosantan), kiseonik, inhibitori fosfodiesteraze-5 (sildenafil), analozi prostaciklina (epoprostenol, treprostans, iloprost), warfarin (kod rekurrentne pulmonalne tromboembolične bolesti);

- sklerodermna reanalna kriza − dijaliza, kratko-delujući inhibitori angiotenzin-konvertujućeg enzima;
- Mano (Manno) i Boin su dali pregled imunomodulatora koji se primenjuju kod SSc prema kategorijama, nazivu leka, mehanizmu dejstva i preporučenim dozama:

  - neselektivna imunoterapija − ciklofosfamid, mikofenolat mofetil, azatioprin, metotreksat;
  - T-ćelijska ciljana imunoterapija − ciklosporin A, antitimocitni globulin, ekstrakorporalna fotofereza, sirolimus (rapamicin);
  - B-ćelijska ciljana imunoterapija − ciklosporin A, antitimocitni globulin, ekstrakorporalna fotofereza, sirolimus (rapamicin);
  - antifibrotična terapija − CAT-192, imatinib mesilat;
  - ćelijski bazirana (cell-based) imunotrapija − transplantacija autolognih i allogenih stem ćelija. Kliničko poboljšanje kod bolesnika sa SSc dobijeno je u pojedinim slučajevima primenom fototerapije UVA 1 zracima.

Zaključak. Podelom sistemske skleroderme u dve grupe oboljenja, grupu difuzne i grupu limitirane skleroderme, sa CREST sindromom kao pripadnikom limitirane skleroderme, mora se imati na umu da obe grupe obuhvataju različite kliničke varijante i različite kliničke značajke. Klinička karakteristika i klinički koraci kod bolesnika sa SSc dobijeni su u pojedinim slučajevima primenom fototerapije UVA 1 zracima.

Ključne reči

Sistemska skleroderma; CREST sindrom; Znaci i simptomi; Dijagnoza; Pregled slučajeva; Pregled literature