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Chapter

Systemic Sclerosis

Murat Borlu and Eda Öksüm Solak

Abstract

Systemic sclerosis (SSc) is a chronic, autoimmune disease which can affect the blood vessels, the visceral organs, and the skin. SSc, most commonly, develops between the ages of 30 and 50, but it can be seen at any age. In terms of skin involvement, SSc can be classified as limited or diffuse. Its etiopathogenesis is still unclear. Microvascular dysfunction is thought to be followed by immunological activation, collagen and extracellular matrix deposition, and finally fibrosis. Diagnosis is based on clinical presentation. Sclerosis of the metacarpophalangeal and/or metatarsophalangeal joints is the major diagnostic criterion, whereas sclerodactylia, digital ulcers (DU), and pulmonary fibrosis are the minor criteria. SSc is diagnosed with one major criterion or two minor criteria. Detection of autoantibodies can help the diagnosis. Antinuclear antibody (ANA), anti-centromere antibody, anti-scl 70, RNA polymerase 1 and 3, and anti-fibrillin antibody can be found positive in SSc. SSc must be differentiated from all sclerosing diseases and the diseases with Raynaud's phenomenon. Visceral diseases, such as primary pulmonary hypertension, primary biliary cirrhosis, and infiltrative cardiomyopathy, should also be considered in its differential diagnosis. The main treatment goal is to target visceral involvement.

Keywords: sclerosis, chronic, microvascular, visceral

1. Introduction

Systemic sclerosis (SSc) is a chronic immune-mediated connective tissue disease, including the skin, inner organs, and blood vessels, with heterogeneous multiple organ involvement whose etiology is unknown. It has two subtypes: diffuse and limited. Its incidence ranges from 4 to 43 million people [1–3] per year, with a prevalence of 88–443 million [4, 5]. It can be seen at any age, though it is most commonly seen in patients aged 30–50 years. The disease shows an earlier onset and a more severe course in black patients [6]. The incidence in women is three to four times higher than in men [6]. Epidemiological studies showed that there is a significant increase in SSc risk in people, whose first-degree relatives have this disease [7].

2. Pathogenesis

The pathogenesis of SSc is not fully known. Disease-triggering agents are some organic solvents (e.g., silica, vinyl chloride, trichloroethylene, epoxy resins, benzene, carbon tetrachloride), some viral diseases (HSV5, CMV), some medications (bleomycin, pentazocine), and radiotherapy [8].

Basic pathogenicities of the disease are microvascular function disorder (vasculopathy) and immune activation, and the final effect of these events is progressive tissue fibrosis with activation of fibroblasts [9].

Vascular disease is observed earliest in SSc pathogenesis. The disease plays an important role in the occurrence of pulmonary artery hypertension, Raynaud's phenomenon, renal damage, and digital ulcers (DU) [10–13]. Raynaud's phenomenon, a typical clinical characteristic of SSc, is a finding characterized by persistent vasospasm and increased adhesion molecules following ischemia and reperfusion attacks [14]. Increased adhesion molecules trigger platelets and neutrophils that bind to endothelial cells and produce superoxide radicals responsible for endothelial cell damage [15]. In addition, an imbalance between vasoconstrictor agents such as endothelin-1 (ET-1) and vasodilating agents such as nitric oxide was observed in SSc, which plays a role in the change of vascular permeability [16]. Increased ET-1 expression plays a role in vascular fibrosis, inflammation, and increased smooth muscle cell proliferation [12]. An impaired cross talk between endothelial cells and perivascular cells may induce an abnormal expression of endothelial growth factor (VEGF), TGF-β, and platelet-derived growth factor (PDGF) in SSc. This may lead to a disruption of peripheral vascularization, which results in fibrosis of the skin and internal organs [17].

It has been determined that Th2 cytokines such as IL 4, IL 5, and IL 13 are oversecreted in SSc patients. It increases IL 4 collagen synthesis and TGF-β production. With IL 13, however, fibroblast activity and TGF-β stimulation are carried out [18]. Also, B-cells produce antibodies and carry out direct fibroblast stimulation via IL 6 [18].

3. Diagnostic criteria and classification

SSc is a heterogeneous disease and this disease spectrum contains different forms. Although the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, telangiectasia) was first defined in 1959,

Criteria	Score
1. Skin hardening of the fingers of both hands spreading proximal to the MKF joints	9
2. Skin hardening of the fingers	
• Puffy fingers	2
• Sclerodactyly (only high scores will be counted)	4
3. Fingertip lesions	
• Digital ulcers	2
• Digital pitting (only high scores will be counted)	3
4. Telangiectasia	2
5. Capillary changes such as abnormal fingernails	2
6. Pulmonary arterial hypertension	2
• Interstitial lung disease (maximum 2 points)	2
7. Raynaud's phenomenon	3
8. SSc-related autoantibodies (anti-centromere, anti-topoisomerase I, anti-RNA polymerase III)	3

Table 1.
ACR/EULAR 2013 systemic sclerosis classification criteria (adapted from source [21]).

it does not fit any classification criteria, and since a subgroup has not been fully defined, it is recommended not to use it nowadays [19].

The criteria published by the American Radiology Associates (ARA) in 1980 have been used for classification for a long time. According to this, symmetrical skin sclerosis in the metacarpophalangeal joint or proximal of the metatarsophalangeal joint is a major criterion, while sclerodactylia, digital atrophic cicatrice, and the loss of finger fat tissue in the distal and bilateral fibrosis in the lungs constitute minor criteria. Diagnosis is possible with the presence of the major criteria or two minor criteria [20]. The ARA criteria do not include patients with limited skin involvement or early SSc and do not involve capillaroscopy/autoantibody tests.

In 2013, the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria were defined. Sensitivity and specificity of these criteria were shown to be higher than the ARA criteria [21]. **Table 1** shows the ACR/EULAR 2013 systemic sclerosis classification criteria. The total score is the sum of the points received from different categories. Patients with a score of nine or higher are classified as definitive systemic sclerosis. However, the use is not recommended in patients with skin thickening that does not involve the fingers, in the presence of scleroderma-like diseases or better clinical pictures.

4. Clinical findings

4.1 Cutaneous involvement

Systemic sclerosis is divided into two subgroups, according to cutaneous involvement: limited systemic sclerosis and diffuse systemic sclerosis. If cutaneous involvement is limited to distal extremities and the face, it is classified as limited systemic sclerosis, and if the involvement is present in the truncus and extremities, it is classified as diffuse systemic sclerosis [22]. Also, systemic sclerosis sine scleroderma, of which 5% of SSc patients are affected, shows typical SSc symptoms but no fibrosis of the skin [23]. Raynaud's phenomenon is seen in more than 90% of SSc patients and is triggered by exposure to cold or emotional stress. It is characterized by white, blue, and red discoloration after triggering and most often affects the hands, feet, tongue, ears, and nose [24].

Cutaneous involvement generally consists of three phases. In the first stage, the edematous phase, non-pitting edema, facial mask appearance, and swelling of the fingers can be seen. After that comes the indurative phase, where the skin hardens and gets a shiny and tense appearance. The last stage is the atrophic phase, characterized by claw hand and sclerodactyly. Sharpening of the nose, thinning of the lips, vertical streaks around the mouth (**Figure 1**), and facial mimic loss may be seen. Skin lines or hyperpigmentation of skin areas exposed to trauma and depigmentation areas on the truncus, face, hand back, and leg fronts may develop. In some cases, the presence of depigmented areas, where perifollicular areas are preserved, results in an appearance of "salt and pepper" on the skin.

In systemic sclerosis disease-specific capillary dilatation, stumps and the presence of avascularity areas can be shown with nail bed capillaroscopy [25]. Sweat and atrophy of the sebaceous gland may lead to dry skin, flaking, and itching. Depending on the calcium accumulation in the skin, hard subcutaneous nodules may appear around the small joints of the hand (calcinosis cutis), which may open to the outside and become ulcers [26]. Ulcers (**Figure 2**) may also develop due to ischemia, trauma, and fibrotic tissue. Telangiectasia is commonly seen in SSc and is stated in the classification criteria [21].

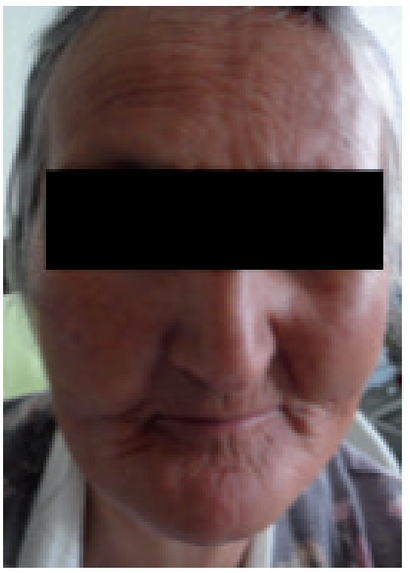

Figure 1.
Nasal sharpening and perioral vertical streaks in a patient.

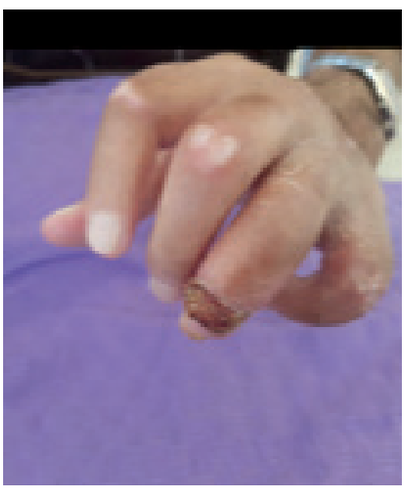

Figure 2.
Digital ulcer in a patient.

4.2 Gastrointestinal system involvement

Ninety percent of scleroderma patients show gastrointestinal involvement. Although it can involve any part of the gastrointestinal tract from the mouth to the anus, the esophagus is the most commonly involved area [27]. The most common complications of SSc in the oral cavity are microstomy and xerostomy. Symptoms of esophageal disease depend on dysmotility and reflux, and related to this, dysphagia, odynophagia, regurgitation, pyrosis, chronic cough, or hoarseness can occur. Stricture, Barrett's esophagus, aspiration pneumonia, and adenocarcinoma may develop as complications in these patients [27, 28]. The two most common symptoms of SSc in the stomach are gastroparesis and gastric antral vascular ectasia (GAVE). A typical striped watermelon appearance is present. Iron deficiency anemia due to GAVE may also be seen [28]. After bacterial growth due to small intestinal involvement, diarrhea and malabsorption or pseudo-obstruction due to hypomotility and dilatation may be observed [28]. Constipation, fecal, rectal prolapse, spontaneous perforation, and colon infarction may develop in the colon and have anorectal involvement [29].

4.3 Pulmonary involvement

Pulmonary involvement, the most important cause of mortality and morbidity in SSc, may occur in the form of interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH) [30].

The highest risk for ILD development is within the first 5 years of the disease. Progressive exercise dyspnea and nonproductive cough are the most common symptoms. Diagnosis is placed with the help of imaging methods and pulmonary function tests. High-resolution computed tomography is a sensitive method in imaging and can show the degree of fibrosis.

Pulmonary artery hypertension affects approximately 15% of scleroderma patients and leads to right heart failure, and the gold standard method for the diagnosis of PAH is right heart catheterization with high pressure in the pulmonary artery [31].

4.4 Musculoskeletal involvement

The most common involvement of the musculoskeletal system in SSc are tendinopathy, joint contractures, and in some cases arthritis. In 45–90% of patients, arthralgia and arthritis of the small joints of the wrist, knees, and ankles occur [31].

Tenosynovitis and tendon ruptures are frequently detected in SSc. Tendon friction sound that can be detected by physical examination is caused by fibrotic deposits in the tendon sheath [32].

Calcinosis and acroosteolysis in the bones (resorption of terminal phalanx) can be seen in SSc patients. These changes are related to digital ischemia [31].

In addition, muscle weakness and pain, which mainly affects the proximal muscles, is another common symptom in SSc. Muscle involvement may occur in the form of myopathy or myositis, and patients should be evaluated from this angle [31]. Muscle weakness may result from nonuse, sedentary life, or joint/tendon involvement or sometimes as a side effect of treatment.

Although respiratory muscle involvement is not common in SSc, respiratory muscles may be affected in SSc-polymyositis/dermatomyositis overlap syndrome [31].

4.5 Cardiac involvement

Cardiac involvement in SSc can be seen in two ways: primary and secondary. Secondary involvement may be secondary to pulmonary arterial hypertension, interstitial lung disease, or kidney disease [33]. Primarily, all layers of the heart, conduction system, coronary vessels, and valves can be involved. Because of these involvements, pericardial effusion, supraventricular or ventricular arrhythmias, conduction disorders, valve regurgitation, myocardial ischemia, myocardial hypertrophy, and heart failure may develop [34].

Because myocardial findings are often faint, especially in the early stage, it is very difficult to detect these patients. However, when the involvement progresses to the symptomatic stage, the patient develops one of the poor prognostic factors [31]. Therefore, early diagnosis of cardiac involvement in SSc is very important. Electrocardiography or echocardiography is not effective in detecting cardiac fibrosis. Magnetic resonance imaging (MRI) is the only method that can detect cardiac involvement in the early stages of the disease. A cardiac MRI can show myocardial inflammation, fibrosis, decreased perfusion of the heart muscle, and ventricular dysfunction [35].

4.6 Renal involvement

Renal involvement in scleroderma is quite common. Even though it appears often as mild renal dysfunction, it can also cause a severe clinical table called scleroderma renal crisis (SRC). The pathogenesis of SRC is not fully known, but studies suggest vasculopathy as a source. Corticosteroids and vasospasm-causing drugs (tacrolimus, cyclosporine, and cocaine) may play a role in the etiology [36]. The risk of SRC development increases in the presence of the autoantibodies anti-RNA polymerase III, anti-topoisomerase I, and anti-U3RNP [36].

Some patients show a chronic clinical table with gradual decrease in eGFR, increase in serum creatinine concentration, proteinuria, hematuria, and moderate arterial hypertension [31].

Decreased glomerular filtration rate, increased serum creatinine, hemolytic anemia, proteinuria, and decreased platelet count are laboratory findings indicating renal involvement [31].

5. Autoantibodies

Antinuclear antibodies (ANA) are 90–95% positive in SSc patients and are the most commonly detected autoantibody. Scleroderma-like diseases should also be considered in the case of ANA negativity. Anti-topoisomerase I (anti-scl 70) antibodies are connected to pulmonary complications, digitals ulcers, and progressive hand involvement. Anti-centromere antibodies are common in limited SSc and positively increase the risk of pulmonary fibrosis and pulmonary hypertension. Anti-RNA polymerase III antibody is associated with renal crisis. Also anti-U3RNP and anti-Th/To antibodies can be detected positively, and the anti-U3RNP antibody increases the risk of pulmonary artery hypertension and cardiovascular complications [37].

6. Histopathology

The diagnosis of systemic sclerosis is placed clinically; therefore biopsy is not recommended routinely [38]. It can be used to rule out other diseases for differential diagnosis. Histologically, excessive collagen accumulation, atrophy of pilosebaceous and eccrine glands, subcutaneous fat loss, and lymphocytic infiltrate are observed. Increased collagen can compress adnexal structures, especially eccrine glands [38].

7. Differential diagnosis

There are many diseases that may trigger dermal sclerosis. The form and character of skin involvement, history of underlying diseases, and chemical exposures are helpful factors in approaching the diagnosis of a patient with skin thickening. Some laboratory studies may be beneficial in verifying imaging and skin biopsy diagnosis [8]. Eosinophilic fasciitis, scleroderma, scleromyxedema, and nephrogenic systemic fibrosis are important in the differential diagnosis of SSc. SSc can be differentiated from other scleroses by the presence of Raynaud's phenomenon, typical distal extremity involvement, nail fold capillary findings, presence of autoantibodies, and internal organ involvement. While the groove mark, which is a recess caused by the withdrawal of subcutaneous tissues along the path of the superficial vessels, favors the eosinophilic fasciitis [39], the detection of monoclonal gammopathy directs

the diagnosis towards scleroderma or scleromyxedema (bbb). Again, if underlying renal failure or gadolinium exposure is detected, the first thought should be towards nephrogenic systemic fibrosis [40].

8. Treatment

The pathogenesis of SSc is still unclear. In recent years, advances have been made in the treatment of the disease, resulting in a prominent improvement in survival rates. The efficient treatment of complications increases the chances of success. Disease duration, complications, and disease activity should be taken into consideration when making therapeutic decisions. The treatment is based on modifying agents and organ-specific drugs [41].

Peripheral vascular involvement frequently occurs as Raynaud's phenomenon. In addition, digital ischemia due to digital vasculopathy, digital ulcers, and associated amputations may be the causes for morbidity in SSc.

Patients with Raynaud's phenomenon should protect themselves from the cold. They also should not smoke and should avoid vasoconstrictor agents. Calcium channel inhibitors (nifedipine, diltiazem, amlodipine) should be the first choice as treatment [41]. Iloprost and other intravenous prostanoids can be used in cases that do not respond to the above. Also, phosphodiesterase type 5 (PDE5) inhibitors may be effective in resistant cases. Selective serotonin reuptake inhibitors, pentoxifylline, prazosin, and endothelin receptor antagonists (ERA) are agents that are less effective and used in selected cases [42].

Early treatment of patients with digital ischemia SSc reduces the risk of morbidity. Intermittent infusion of prostacyclin or analogs was found to be effective in the treatment of RF and ischemic digital ulcer [41]. Sildenafil and bosentan are recommended for the treatment of digital ulcers that developed due to unsuccessful treated systemic sclerosis with calcium channel blockers and prostanoid therapies [41]. There are also uncontrolled studies suggesting that atorvastatin, vitamin E, and intravenous N-acetylcysteine may be beneficial. Mesenchymal stem cell therapy is one of the developing methods in the treatment of DU [43].

The first choice for the treatment of pulmonary artery hypertension is phosphodiesterase type 5 inhibitors (e.g., sildenafil or tadalafil) or endothelin receptor antagonists such as bosentan and macitentan. If those are not effective, prostanoids may be added to the treatment [44]. Prostanoids are the first choice in severe cases. If there is no response, combination treatments can be applied. Recently, the guanylate cyclase agonist riociguat has been involved in treatment [41].

The treatment of interstitial lung disease patients is based on immunosuppressive drugs. The first preferred agent is oral mycophenolate mofetil (MMF). One of the applied treatment regimens for nonresponsive patients is the administration of cyclophosphamide (CYC) orally at doses of 1–2 mg/kg/day or iv 600 mg/m^2/month. After the disease activity has been taken under control, it is recommended to continue treatment with azathioprine at a dose of 2.5 mg/kg/day [41]. In selected patients, rituximab (RTX, anti-CD20 monoclonal antibody) can be used as an alternative treatment [41, 45].

Immunosuppressants such as methotrexate (MTX), cyclophosphamide, and mycophenolate mofetil are commonly used in fibrosis of the skin [31]. If the treatment is unsuccessful or if these drugs cannot be used for whatever reason, low-dose systemic corticosteroids or rituximab may be preferred [31]. The effect of D-penicillamine, which has been used for many years, is controversial [46].

In systemic sclerosis, exertional dyspnea, tachycardia, and chest pain may occur due to myocardial involvement. Selective beta-blockers are effective in this kind

Organ involvement	Recommendation	Strength of recommendation
Raynaud's phenomenon	• Calcium antagonists	A
	• PDE-5 inhibitors	A
	• Prostanoids	A
	• Fluoxetine	C
Digital ulcers	• Intravenous iloprost	A
	• PDE-5 inhibitors	A
	• Bosentan*	A
Pulmonary arterial hypertension	• ERA, PDE-5 inhibitors, riociguat	B
	• Intravenous epoprostenol	A
	• Other prostacyclin analogs (iloprost, treprostinil)	B
Skin and lung disease		
Skin	• Methotrexate	A
Lung disease	• Cyclophosphamide	A
	• HSCT	A
SRC	• ACE inhibitors	**C**
	• **Glucocorticoids are associated with a higher risk of SRC	**C**
Gastrointestinal disease	PPI	B
	Prokinetic drugs	C
	Antibiotics	L

ERA, endothelin receptor antagonists; HSCT, hematopoietic stem cell transplantation; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; PPI, proton pump inhibitor; SRC, scleroderma renal crisis; SSc, systemic sclerosis; RP, Raynaud's phenomenon.
**Treats and reduces the formation of new ulcers.*
***Blood pressure and renal function should be carefully monitored in SSc patients treated with glucocorticoids.*

Table 2.
The updated EULAR recommendations for treatment of systemic sclerosis.

of symptoms [33]. If cardiac tamponade develops due to pericarditis in cardiac involvement, treatment becomes more difficult. The patient may not respond to systemic corticosteroid therapy, and drainage treatment may become necessary [47]. Some SSc patients may develop microvascular ischemia due to vasospasm of small coronary arteries and arterioles, also called cardiac Raynaud's phenomenon. Nifedipine treatment is quite effective in such patients [48].

SSc patients with GI involvement of dysphagia, pyrosis, esophageal reflux, esophagitis, distention, abdominal pain, and diarrhea can be treated with proton pump inhibitors (PPI), prokinetic drugs, and intermittent antibiotics (gg). Patients that developed gastric antral vascular ectasia may have severe upper GI bleeding. Here, supportive treatment and endoscopic treatment methods can be used. Surgical antrectomy becomes necessary as the last resort in resistant cases [49].

The first choice for patients with scleroderma renal crisis is a high dose of angiotensin receptor antagonists (ACE-I). It was determined that this treatment significantly decreased mortality [31]. In cases with insufficient response, angiotensin receptor blockers (ARB) and calcium channel blockers may be combined with ACE-I treatment of nitrates [31]. Beta-blockers are not recommended due to

their vasoconstriction enhancing effects. Hypotension should be avoided, and close monitoring should be performed for patients using systemic steroids since they significantly increase the risk [50].

The updated EULAR recommendations for the treatment of systemic sclerosis are summarized in **Table 2**.

9. Result

As a result, we should not forget that systemic sclerosis is a chronic disease that can cause serious morbidity and mortality and that placing a diagnosis can be difficult from time to time. The disease does not have a specific treatment. The patient should be evaluated according to involved systems and clinical table. In addition, early diagnosis and early initiation of treatment increase the chances of efficacy. A better understanding of the pathogenesis may lead to the development of more successful and specific treatment methods.

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