SYSTEMIC SCLEROSIS

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ABSTRACT

Systemic sclerosis (SSc) is a rare connective tissue disease of unknown etiology, heterogeneous clinical manifestations, and chronic evolution, often progressive.1,6 It is characterized by inflammatory, fibrotic, and atrophic changes.6 The onset of the disease is more common in the age group of 30 to 50 years, and is more prevalent in women. SSc has been reported in all geographic areas and in all races, but it has been observed that the black race has a higher chance of developing it.[1.4]

SSc can compromise the connective tissue of various organs such as the skin, lungs, heart, gastrointestinal, renal and musculoskeletal tracts.8 In addition, it is classified into two subtypes, the diffuse and limited forms, and it is the extent of skin thickening that differentiates these two. In 10% of patients, the skin is normal, no thickening occurs, and it is called scleroderma sine sclero.[4]

As it is a disease that affects multiple systems, it imposes limitations on the affected individual and affects their quality of life. Proper diagnosis is very important, since the manifestations can be varied and with some possible differential diagnoses.[4]

Keywords: Sclerosis. Connective tissue. Sickness.

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INTRODUCTION

EPIDEMIOLOGY

Systemic sclerosis (SSc) is a rare diffuse connective tissue disease of unknown cause. Its prevalence is higher among females, about 3-14 times higher than in men, and is more common in the reproductive age group, declining after menopause (suggesting the influence of sex hormones). It is a pathology that can present at all ages, but its onset occurs more in the 30 to 50 age group, both in limited and diffuse cutaneous form. In addition, it can affect all races, although it is higher in blacks. It has been observed that this group is more likely to develop a diffuse cutaneous form, associated with interstitial pulmonary involvement, characterizing a worse prognosis.[1,2]

Its distribution is worldwide, with incidence varying according to countries. In the United States, 19 to 75 cases per 100,000 inhabitants were estimated, while in England, Japan and Australia the rates were lower. England had the most similar percentage, about 1 patient for every thousand inhabitants.[1,3] According to some analyses, it has been observed that regional genetic variations and environmental exposures can influence prevalence and incidence rates.[3]

There are no published data on the predominance of systemic sclerosis in the Brazilian population,[1,3] but a specific study analyzed the incidence of this disease in the city of Campo Grande, capital of the state of Mato Grosso do Sul. A total of 166 patients with SSc were treated in the city's outpatient clinics and rheumatology services, among which 89 lived in the city, only 10 were new cases and 79 had already been previously diagnosed. Thus, the prevalence in 2014 in this region of Brazil was 105.6 per million inhabitants. Furthermore, it is curious that among these 89 patients, 86 were women, and 58 were white, 20 brown, 8 black and 3 yellow.[3]

A genetic contribution to susceptibility to the disease has already been observed, as 1.6% of patients with SSc have a first-degree relative with SSc, thus observing a higher prevalence than in the general population. The risk of other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, is also higher.[1]

ETIOLOGY AND PATHOPHYSIOLOGY

Systemic sclerosis is a disease of unknown etiology with a probable multifactorial cause, including environmental and genetic factors.[2] Some possible factors involved in the pathogenesis of this disease are: solvents (e.g., benzene), toxic oil and silica, drugs, breast reconstruction with silicone prosthesis, viruses (retrovirus, human parvovirus B19, and

cytomegalovirus), and genetics. It is believed that some viruses have the same sequence as the topoisomerase 1 protein, which is targeted by SSc.[1,4]

The pathophysiology of systemic sclerosis can be explained through three important aspects: vascular dysfunction, immune and fibroblast activation, with excessive collagen production.[1,5] The heterogeneity in the clinical characteristics of SSc patients is probably a reflection of the variable contributions of each of these pathogenic factors.

Vasculopathy is very important in the clinical practice of systemic sclerosis, and its origin is due to the injury and activation of endothelial cells, due to unknown factors. Raynaud's phenomenon is an example of an early manifestation, which is characterized by an altered blood flow response brought on by cold.[1,5]

With the injured endothelium, there is a dysregulation of vasodilatory substances (such as nitric oxide and prostacyclin) and vasoconstrictors (endothelin-1). The increase in serum endothelin stimulates collagen synthesis, increases leukocyte adhesion to the endothelium, promotes migration and proliferation of smooth muscle cells to the intimal layer of the vessels, activating fibroblasts. This process leads to the synthesis of extracellular matrix molecules, leading to fibrosis with loss of elasticity and reduction of the vascular lumen, causing hypoxemia and tissue necrosis. The increase in nitric oxide, in turn, helps to maintain muscle tone, as it counterbalances the action of endoletin-1.[4] In this way, there is a greater expression of the intracellular adhesion molecule-1 (ICAM-1) and others.[1,4]

In the microvessels, an increase in leukocyte permeability and diapedesis, activation of the coagulation and fibrinolytic cascade, as well as platelet aggregation, are observed. This, in turn, stimulates the release of serotonin and platelet granules (such as thromboxane). In addition, the process of vasculopathy also affects the great vessels in various organs, resulting in reduced blood flow and tissue ischemia.[1]

Another factor is the involvement of both the humoral and cellular immune systems, in which mediators make the link between vasculopathy and tissue fibrosis. In the early stages of the disease, activated T cells, monocytes, and macrophages accumulate in lesions of the skin, lungs, and other affected organs. These in turn show a TH2 polarized immune response, and secrete IL-4 and IL-13, these cytokines induce TGF-beta production, promote collagen synthesis and other pro-fibrosis responses.[1,4] Approximately 95% of patients with systemic sclerosis have circulating autoantibodies against one or more antigens, these include anticentromere, antitopoisomerase I, antifibrillaryn, anti-PM-Scl, or anti-RNA polymerase I or III. Although antitoisomerase-I antibodies are not very sensitive,

they are highly specific for SSc (98-100%) and are related to a higher risk of interstitial lung disease and skin lesion.[6]

The last process is the most striking due to the intense deposit of collagen, fibronectin and glycosaminoglycans in the tissues involved.[4] Fibroblasts are mesenchymal cells responsible for maintaining the functional and structural integrity of connective tissue. With the production of TGF-beta, these proliferate, migrate, and secrete collagens, extracellular matrix, growth factors, and cytokines, in addition to differentiating into myofibroblasts. Fibroblasts in SSc exhibit an abnormally cultured phenotype and have an increased rate of collagen gene transcription, thus having large amounts of this substance.[1.4]

CLINICAL PICTURE

Systemic sclerosis has two forms of presentation, limited cutaneous and diffuse cutaneous. The limited form is marked by a slower evolution, characterized by skin thickening restricted to the extremities of the limbs and face, and is typically associated with the presence of anti-centromere antibody.[4,8] Pulmonary arterial hypertension is an expected complication. In the diffuse form, the thickening occurs early and extends to the proximal region of the limbs, trunk and abdomen. Pulmonary fibrosis and scleroderma renal crisis are more frequent in this case, and the predominant antibodies are anti-Scl70 and anti-RNA polymerase III.[8] A minority presents typical signs and symptoms of SSc, but without cutaneous involvement, and is classified as sine scleroderma.[8]

The clinical picture will be divided according to the classification of the disease, and the main manifestations are:

Cutaneous: the onset of the disease is associated with the first phases of cutaneous involvement, marked by edema (puffy fingers) representing the inflammation generated and by hardened regions (after regression of edema), and there may be intense itching. Fibrosis is characterized by thickening of the skin, being the mark that most distinguishes systemic sclerosis from other connective tissue pathologies.[1,8] Usually this process begins in the extremities, fingers and toes. As the disease progresses, there may be thinning of the lips and retraction of the gums, leading to microstomia and dental prominence.[8] The modified Rodnan score is used to measure the extent, degree of skin involvement, and prognosis of the disease. Finally, skin atrophy occurs. Due to the accumulation of collagen, obliteration of the hair follicles, sweat glands, eccrine and sebaceous glands can occur, resulting in hair loss, decreased sweating and dry skin.[1] Among the most common alterations, it is possible

to observe hyperchromia lesions in the extremities and trunk, or hypopigmented, especially in dark-skinned patients, known as salt and pepper lesions. In addition, telangiectasias and calcinosis may occur.[1,6,8]

Vascular: Raynaud's phenomenon is an episodic vasoconstriction in the fingers and toes, which occurs in practically all patients with systemic sclerosis (95%), and is caused by cold and stress.[1,6] Generally in the limited forms of the disease, this process precedes the cutaneous or visceral manifestations by years, while in the diffuse forms, it occurs together. This phenomenon, when associated with SSc, can bring complications, such as scars, digital ulcers, and even amputation of the fingers.[6]

Gastrointestinal: involvement of the entire gastrointestinal tract (from the oropharynx to the anus) may occur, and affects about 90% of patients with SSc.[6] The esophagus is the most affected organ (esophagitis), and therefore complaints of dysphagia, odynophagia, retrosternal burning pain, and regurgitation are common.[4] Abnormal peristalsis and relaxation of the lower esophageal sphincter aggravate esophagitis due to reflux, facilitating Barrett's metaplasia, and follow-up with upper gastrointestinal endoscopy is extremely important.[4,8] Intestinal and gastric involvement are less frequent.[6]

Musculoskeletal system: arthralgias, arthritis, and morning stiffness are the most frequent symptoms, especially in the early stages of the disease.[4] Muscle weakness and tendon friction occur due to the inflammation generated, and are more present in the diffuse cutaneous form. In addition, joint contractures can lead to the classic scleroderma claw hand.[8]

Pulmonary: pulmonary involvement is the main cause of morbidity and mortality in systemic sclerosis. It is very common, even in asymptomatic individuals, being present in approximately 90% of patients with SSc without respiratory symptoms, and changes are observed by computed tomography.[8]

Cardiac: cardiac involvement occurs in two ways, when it is primary, inflammation and fibrosis are observed, leading to myocardial ischemia, fibrosis, myositis, pericarditis and heart failure. When it is secondary to pulmonary arterial hypertension, there is right and left heart failure, tricuspid regurgitation, diagnosed by transesophageal Doppler echocardiography.[6] It usually occurs in the diffuse and asymptomatic form.[4]

Renal: it is rare to happen, and can present a difficult prognosis. Scleroderma renal crisis is characterized by the development of thrombotic microangiopathy and a sudden

onset of severe arterial hypertension, associated with progressive renal failure.[4,8] Some symptoms that may occur are headache, visual disturbances, encephalopathy, seizures, pulmonary edema, and pericardial effusion.[6]

DIAGNOSIS

Systemic sclerosis is a disease in which anamnesis and physical examination are essential, and in 90% of cases it is necessary for diagnosis. For this, it is necessary to be aware of the varied range of cutaneous, vascular and visceral manifestations. Laboratory and imaging tests are important for the evaluation, monitoring of the disease, and therapeutic planning of the patient.[4.3]

There are some ways of stratifying SSc through classification criteria. The most used in clinical practice are those of the American Rheumatism Association (ACR), which was proposed in 1890, and from this it is possible to make a standard definition of the disease, in which it considers SSc in the presence of a major criterion or at least two minor criteria.[2.3]

- Major criterion: proximal scleroderma (symmetrical fibrosis of the skin proximal to the metacarpophalangeal (MCF) or metatarsophalangeal (MTF).
- Minor criteria: sclerodactyly, ulcerations of digital pulps or resorption of distal phalanges, fibrosis in the lung bases (present on chest X-ray).

In patients with the disease in the initial phase, the above criteria do not detect adequately, and for this reason others have been created to facilitate the diagnosis of early forms: [2,3]

- Objective evidence (physician-observed) of Raynaud's phenomenon plus standard scleroderma on nailfold capillaroscopy or SSc-specific autoantibodies (anticentromere, antitopoisomerase I, antifibrillaryn, anti-PM-Scl, or anti-RNA polymerase I or III).
- Subjective evidence (at anamnesis) of Raynaud's phenomenon plus scleroderma pattern on nailfold capillaroscopy or SSc-specific autoantibodies.

To help, some complementary tests can be requested, including laboratory tests, in order to evaluate autoantibodies (ANA and disease-specific tests). ANA is an antinuclear antibody, and its positive value is expected in most patients (95%),[4,6] its most common pattern in immunofluorescence is nucleolar. Its absence imposes a differential diagnosis with diseases that simulate SSc, such as: eosinophilic fasciitis, nephrogenic systemic fibrosis, and scleromyxedema.[6] The disease-specific antibodies are: anticentromere

antibody (ACA), antitopoisomerase 1 antibody (Scl-70), antibodies against RNA polymerase I, II, and III, and fibrillarin.[4]

Antibodies against topoisomerase I are detected in 31% of patients with diffuse cutaneous SSc, but in only 13% of patients with limited cutaneous SSc, while anticentromere antibodies are the opposite, they are detected in 38% of patients with limited cutaneous SSc and only in 2% of patients with diffuse cutaneous SSc. [1.8]

In addition, autoantibodies are related to the patient's clinical practice, such as anticentromere antibodies are commonly associated with limited cutaneous SSc and pulmonary arterial hypertension, and rarely with cardiac and renal involvement, presenting a better survival (Figure 2). Patients positive for topoisomerase I have reduced survival compared to those without this antibody.[1.2]

Laboratory tests are also useful for the evaluation of the disease and the patient, for which the erythrocyte sedimentation rate, C-reactive protein, for example, and the characterization of systemic involvement are analyzed.[6]

Imaging tests help early recognition, adequate classification and extension of the involvement of different organs in patients with SSc. Examples of what can help are pulmonary function tests that show whether there is a progressive decrease in total lung capacity and reduced carbon monoxide diffusion. The reduction in carbon monoxide diffusion in the absence of restriction on spirometry is very suggestive of pulmonary hypertension. High-resolution chest tomography is the most sensitive test to detect interstitial lesions. Ground-glass images of the lung bases are the most common lesions, but in addition, honeycomb images, reticular opacities, and cysts can be observed. Transthoracic echocardiogram should be done to investigate pulmonary hypertension. Upper GI endoscopy is important to evaluate the gastrointestinal tract, especially the esophagus.[4.6]

The presence of skin hardening with a characteristic symmetrical distribution pattern is very common in cutaneous systemic sclerosis, for this reason a full-thickness skin biopsy is necessary to establish the diagnosis.[1] Nailfold capillaroscopy (CPU) is a non-invasive, low-cost imaging method that is of great help in this approach. This allows an evaluation of the structural alterations of the peripheral microcirculation, and is used mainly to differentiate between primary and secondary Raynaud's phenomenon and in the diagnosis of SSc. Approximately 90% of patients with SSc have the SD (scleroderma pattern) in the CPU, characterized by the presence of variable intensity of capillary dilations and devascularization.[8]

Figure 1: Autoantibodies and clinical correlation in SSc.

Autoanticorpos	Correlação clínica
Acometimento cutâneo difuso	
Anti-DNA topoisomerase I (Scl-70)	Doença intersticial pulmonar. Pior prognóstico
Anti-RNA polimerase III	Crise renal esclerodérmica e neoplasia. Pior prognóstico
Antifibrilarina (U3 RNP)	HAP e miosite
Anti-Pm/Scl	Doença intersticial pulmonar, síndrome de sobreposição e miosite
Acometimento cutâneo limitado	
Antiproteínas centroméricas	Úlcera digital, telangiectasias e HAP
Anti-U1 RNP	DMTC, HAP

Source: Zarur, 2020

TREATMENT

The therapeutic approach to systemic sclerosis should be based on the extent and severity of the manifestations presented. General measures should be adopted by the in a multidisciplinary manner, among them we have smoking cessation, protection from exposure to cold, vaccination for influenza and pneumococcus, anti-reflux measures, nutritional support and physical activity.[6]

Advanced diagnosis has provided early identification of cases, and this is very valid for cases of diffuse cutaneous SSc, in which treatment with immunosuppressants would help prevent progression to cutaneous and pulmonary fibrosis.[6]

In general, treatment for cutaneous involvement (depending on the severity) can be performed with immunosuppressants, such as methotrexate, (the drug of choice for the patient in the report above). In the diffuse cutaneous form and when there is a risk of internal organ involvement, the use of mycophenolate or intravenous pulse therapy with cyclophosphamide is feasible.[4.6]

For Raynaud's phenomenon, the first line of treatment is calcium channel blockers, and phosphodiesterase 5 inhibitors, fluoxetine, losartan and venous prostanoids can also be used.[6]

Treatment of gastrointestinal manifestations can be done with proton pump inhibitors, H2 receptor antagonists, prokinetics, and antibiotics for cases of bacterial overgrowth.[6]

For joint manifestations, low doses of prednisone and/or methotrexate are good options.[4.6]

Pulmonary arterial hypertension (PAH) can be treated with vasodilators such as phosphodiesterase 5 inhibitors (sildenafil, tadalafil), endothelin 1 receptor antagonists (bosentan, ambrisentan), and prostanoids.[4.6]

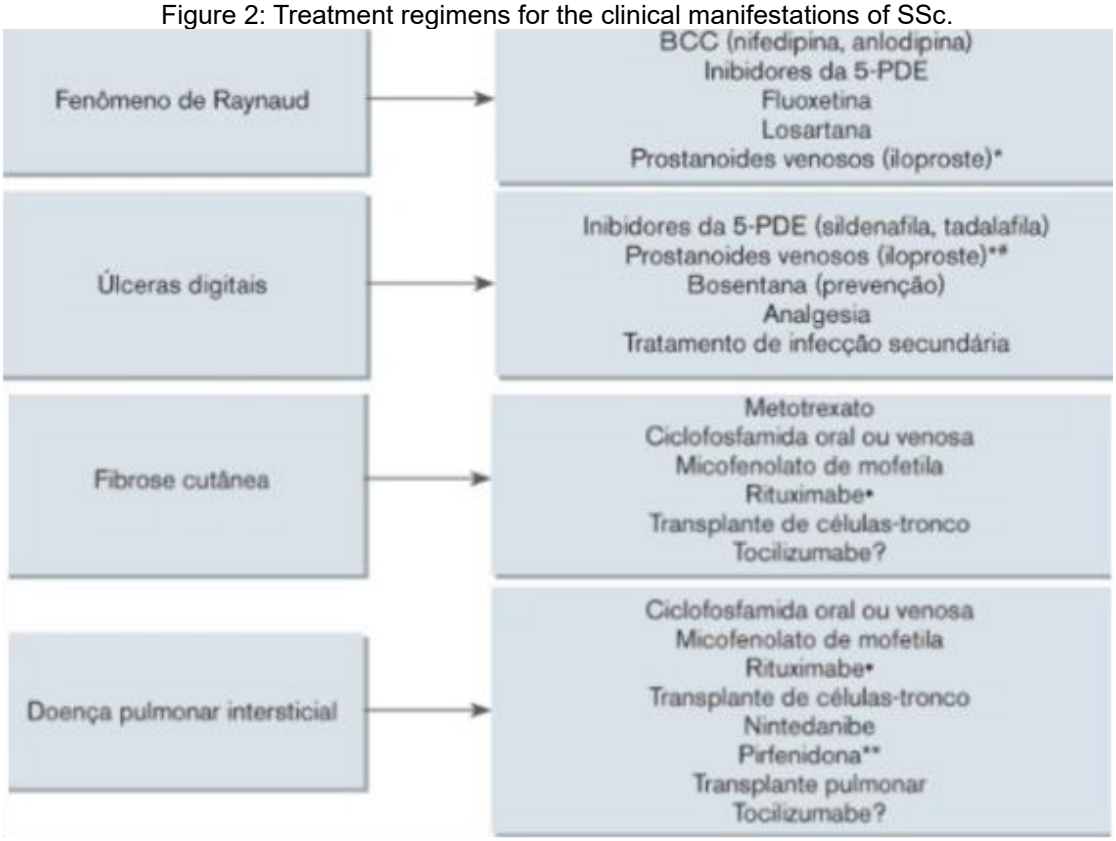
Interstitial lung diseases should be treated with monthly or oral intravenous cyclophosphamide, or with mycophenolate as induction treatment. The maintenance phase can be performed with mycophenolate or azathioprine. In refractory cases, rituximab is a possible option.[8]

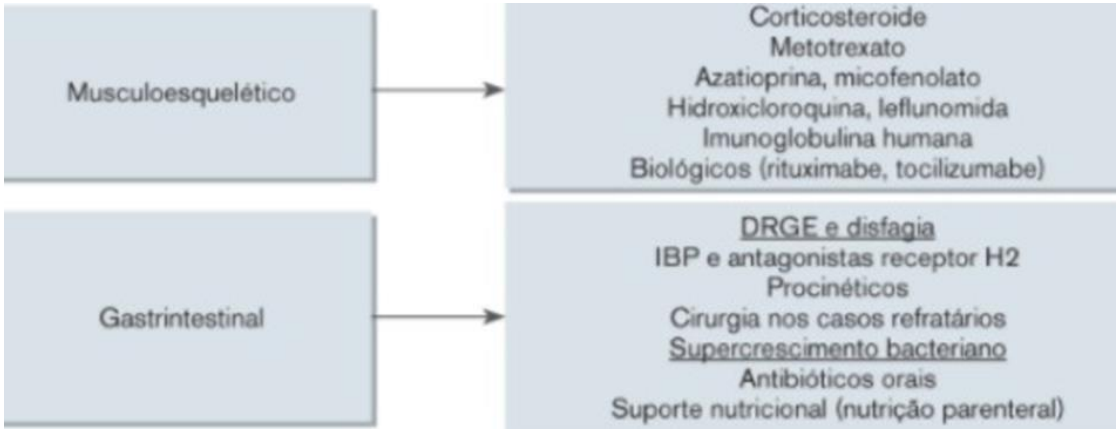
In symptomatic pericarditis, the use of non-steroidal anti-inflammatory drugs or low doses of corticosteroids are sufficient. In patients with large strokes, pericardiocentesis may be necessary.[4]

In scleroderma renal crisis, treatment can be done with high-dose ACE inhibitors (e.g., captopril). [4.6]

The table below summarizes the main treatment strategies according to the clinical manifestation presented by the patient.

Figure 2: Treatment regimens for the clinical manifestations of SSc.





Source: Freire, 2021

CONCLUSION

As seen in the course of this study, systemic sclerosis can affect the patient's quality of life, due to its wide and complex network of clinical manifestations, which makes the diagnosis challenging. We can conclude that systemic sclerosis is a pathology of great importance for medicine, and that there are still many clinical studies that seek new measures to bring more benefits and long-term survival.

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