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Mini Review

Signs and Symptoms of Systemic Sclerosis

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Abstract

Systemic sclerosis is a chronic autoimmune disorder characterized by thickening of the skin caused by accumulation of collagen and extracellular matrix proteins, and by injury to small arteries. The systemic manifestations of the disease are diverse and encompass various degrees of severity. Major signs and symptoms are related to peripheral vascular disease, lung parenchymal, pulmonary artery, digestive tract, kidney and musculoskeletal involvements. In tissues, both ischemic and fibrotic lesions are observed.

In this review, we aim to synthesize the main symptoms related to the organ dysfunction that leads to disability and morbidity for patients. Prognosis is determined by the extent and distribution of skin involvement (which defines the limited or diffuse cutaneous form) and the internal organ involvement. Death is most often caused by lung, heart, and kidney involvement. Physicians should assess potential involvement of these organs when systemic sclerosis is suspected. Although not life-threatening signs, physicians must be also aware that when patients are questioned, the two major declared complaints concern facial and hand disabilities. Hands and face are almost always affected, clinically obvious and hard to conceal, leading to disability and a decrease in quality of life. These manifestations represent a large burden on patients' daily activities with social and psychological discomfort. They both represent a priority for patients who often feel that these features are neglected.

INTRODUCTION

Systemic Sclerosis (SSc) or Scleroderma is a rare autoimmune disease characterised by hardening and thickening of the skin, which explains the name "sclerosis of the dermis". Sclerosis does not only affect the skin but also harms internal organs, particularly the lungs where fibrosis can extend to the whole lung parenchyma and become life-threatening condition. Beyond the skin, other structures can be affected, such as the blood vessels with anomalies of the vascular tone, clinically illustrated by the Raynaud's phenomenon. Vascular involvement is not only functional but also structural and can lead to progressive obliterative vasculopathy, leading to ischemic digital ulcers. The involvement of the pulmonary artery vascular wall leads to pulmonary arterial hypertension which is another life-threatening condition for SSc patients.

SSc belongs to the group of orphan diseases (Orpha number ORPHA801). SSc differs from other autoimmune diseases by 1/ excessive collagen accumulation and scarring (fibrosis) of the skin and internal organs, 2/abnormal vasomotor tone and obliterative lesions, 3/ SSc-related autoantibody production, the latter being used among other clinical features to ensure the diagnosis.Systemic sclerosis has traditionally been considered a disease of tissue fibrosis, but it is now recognized that vascular alteration plays a fundamental and probably initial role in pathogenesis and clinical burden. It is now acknowledged that the vascular disease can be subclinical within years before the final clinical outcome is expressed.

The prevalence of SSc is estimated at around 15-25/100,000. Women are predominantly affected (F/M sex ratio around 4:1 to 14:1).The peak incidence is observed between the third and fifth decade of life. There is still no cure for SSc. The exact etiology is still unknown but immune dys regulation with cytokines and growth factors production, auto antibodies, micro chimerism (all reactive T cell from a child surviving for a long time in the mother's body and *vice versa*), genetic, and environmental factors are known for their roles in disease occurrence.

CLINICAL CHARACTERISTICS

The heterogeneity of this disease is notable. Signs and symptoms differ depending on the extent of skin sclerosis, severity of the vasculopathy and type of organ involvement. The esophagus, lungs, heart, and kidneys are the most frequent targets. Thus, patients' severity highly depends on the number of affected organs and the degree of their alteration.

Skin manifestations

Skin involvement is the hallmark feature of SSc. It is characterized by variable extent and severity of skin thickening and hardening. The fingers, hands, and face are generally the earliest areas of the body to be involved. Patients are sub-

classified into the diffuse cutaneous form of SSc (dcSSc) when skin thickening extends to the trunk and the proximal part of the limbs, and into the limited cutaneous form (lcSSc) when skin in duration is limited to face, hands and feet. In very rare cases, visceral disease occurs without skin involvement, and is called SSc sine scleroderma.

Cutaneous changes usually begin with an early phase of skin oedema, manifested as swollen fingers and hands (Figure 1). In dcSSc, these changes are followed by the development of firm, thickened skin over the fingers (sclerodactyly) and the hands (Figure 2), trunk, and face.

The patients in whom sclerotic changes develop more rapidly are at greater risk of serious organ involvement such as pulmonary fibrosis and renal failure. Skin thickening typically peaks in the first 3 to 5 years. Skin thickening may then begin to regress slowly over time. As a result of skin thickening, flexion contractures can develop over joints, and can lead to hand deformity (Figure 3).

Other encountered skin manifestations include: pruritus, particularly on the sclerotic skin, pigmentation abnormalities of the skin with hyper pigmentation on white skin or hypo pigmentation on black skin ("salt-and-pepper", Figure 4).

Telangiectasias (macroscopically visible dilated skin vessels) that occur primarily on the hands and face are a prominent feature in scleroderma present in the majority of patients (Figure 5).

Mouth disability, aesthetic changes, and impairment of the patient's self-image, nearly concern all of the patients suffering from SSc. The face becomes amimic, vertical furrows develop around the mouth due to retraction of the skin, and the nose becomes sharp (Figure 6). *Other changes consist in telangiectasia* on the face, lips or the inside of the mouth, hypo pigmentation and hyper pigmentation, sicca syndrome, and thinning and reduction of mouth width (microcheilia) and opening (microstomia) (Figure 7).These changes interfere with eating, speaking and oral hygiene activities. Indeed, dental problems are common for people with scleroderma due to tightening facial skin making the mouth opening smaller and narrower, dry mouth caused by salivary gland damage and damage to connective tissues in the mouth leading to lose teeth.

Calcinosis cutis consists of abnormal calcium deposition in soft tissues. Calcinosis often has an acral distribution (digits, elbows, and knees), causing pain, local inflammation, irritation, muscle atrophy, ulceration with the possibility of secondary infection, and joint contractures. Disabling masses called "tumoralcalcinosis", located in nearly all joints can also occur in around one third of patients, leading to severe disability (Figure 8).

Vascular manifestations

Vascular dysfunction is a significant component of the pathogenesis of SSc. The most characteristic clinical manifestation of vascular dysfunction of SSc is Raynaud's phenomenon, an episodic, reversible sequential expression of pallor, cyanosis, and redness of the digits occurring as an attack in response to cold exposure, temperature variation or emotions (Figure 9). In

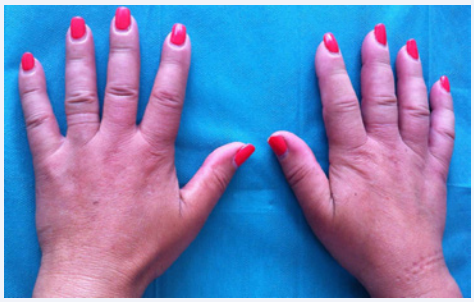

Figure 1 Swollen fingers and hands, with a persisting mark of the ring and the bracelet.

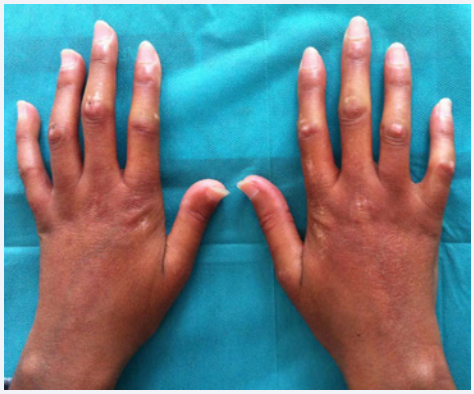

Figure 2 Sclerodactyly with tight skin on the fingers on the dorsal hand.

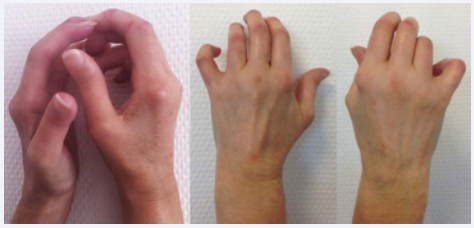

Figure 3 Hands in claw.

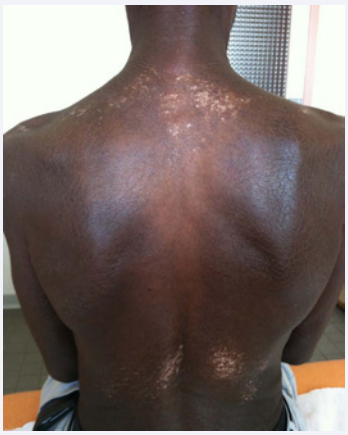

Figure 4 Hypopigmentation of skin patches on a black skin.

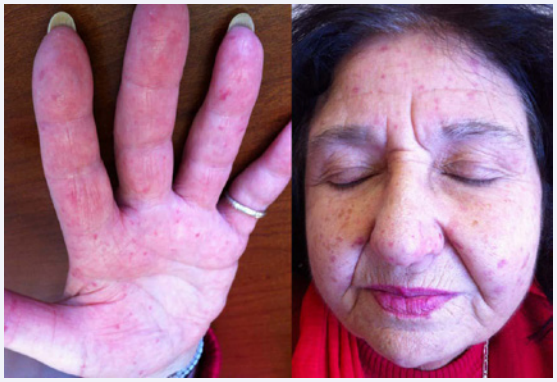

Figure 5 Telangiectasia on hands (on the left) and face (on the right) of the same patient with a limited cutaneous form of the disease.

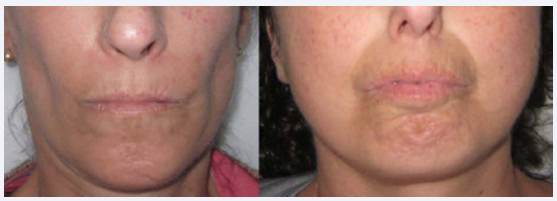

Figure 6 Vertical furrows around the mouth.

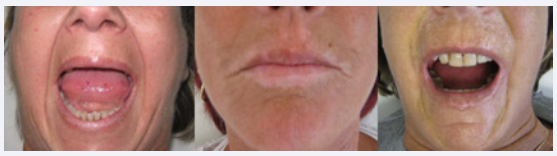

Figure 7 Telangiectasia on the tongue (on the left), hypo pigmentation around the lips(center) and mouth opening limitation (on the right).

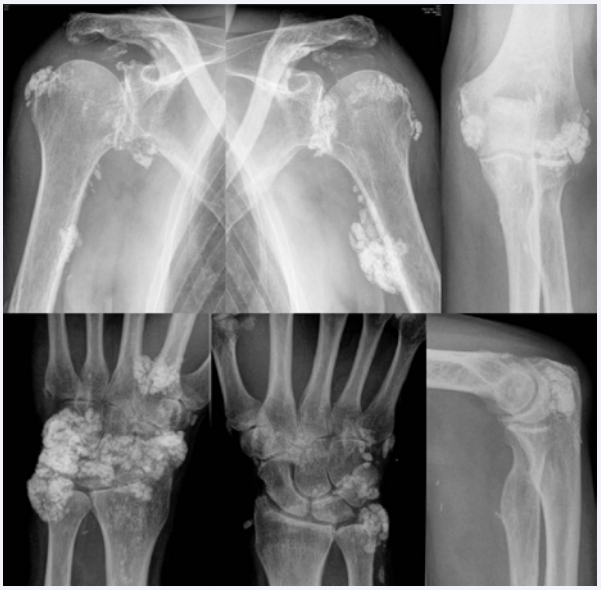

Figure 8 Soft tissue calcinosis of the scapula-humeral joint and next to the humerus, the elbows and wrists.

some occupational or leisure activities, vibrations and the use of vibrating tools, can be an additional cause of Raynaud's attacks. Raynaud's phenomenon affects almost all patients and is often the earliest manifestation of the disease. In patients with lcSSc, it may be present for years before clinically significant skin changes and internal organ involvement development. Although some patients with Raynaud's phenomenon may not develop the entire spectrum of triphasic color changes (pallor, cyanosis, and red engorgement), most have digital pallor in response to cold or stress.

Nail fold capillaroscopy (optic device or video capillaroscopy which offers a better image acquisition) is an essential imaging technique used in the evaluation of microcirculation and is one of the best diagnostic tools for the early detection of SSc. Capillaroscopic abnormalities typical of SSc include enlarged capillaries and capillary loss with or without capillary haemorrhages. The latter can be observed on attentive finger examination (Figure 9). Capillaroscopy identifies morphological patterns specific to various stages of SSc, named "Early", "Active" and "Late" patterns. The "Early" SSc pattern is characterized by few enlarged and giant capillaries, capillary haemorrhages, no evident capillary loss and a relatively well preserved capillary distribution. The "Active" SSc pattern, is characterized by frequent giant capillaries, frequent capillary haemorrhages, moderate capillary loss, absent or mild ramified capillaries and a mild disorganization of the capillary architecture. In the "Late" SSc pattern, giant capillaries and haemorrhages are few or absent; there is irregular enlargement of the capillaries, severe capillary loss with evident extensive a vascular areas, ramified or bushy capillaries and a disorganization of the capillary array.

Digital ulcers (DUs), defined as necrotic lesions that occur in up to 50% of patients with limited or diffuse SSc. Two types of DU may be distinguished: - "ischemic" DUs that are most frequently located on distal areas of fingers, involving pulp or sometimes lateral edges (Figure 10), and - "mechanical" DUs occurring at bony prominences, usually at meta carpophalangeal or inter phalangeal joints of the fingers, promoted by micro traumatic events and by traction exerted on the scleroses skin when the fingers are flexed (Figure 10). Multiple types of DUs can coexist in the same patient. Potential complications include infections, digital necrosis (Figure 11) and gangrene. DUs frequently lead to pitting scars, a characteristic feature of the disease (Figure 11). In 43% of patients, ischemic DUs are observed within 1 year after

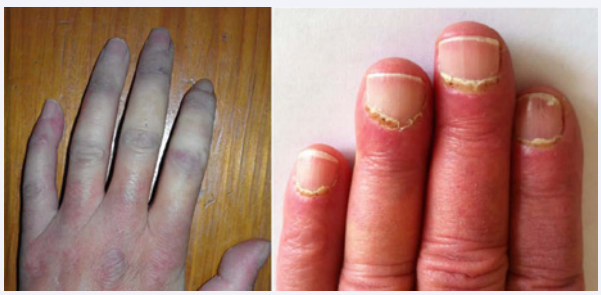

Figure 9 Hypoxic and cyanic phases of a Raynaud's phenomenon crisis (on the left) and hyperkeratosis with hemorrhages on the nail folds (on the right).

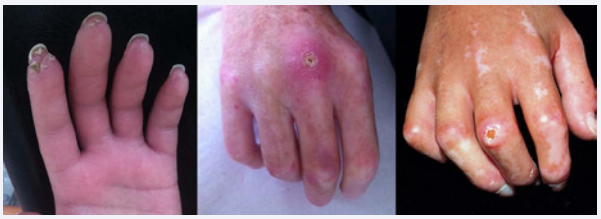

Figure 10 Ischemic digital ulcer (on the left) and mechanic ulcers (on the right).

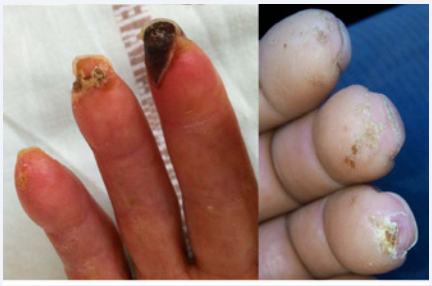

Figure 11 Digital necrosis (on the left) and pitting scars(on the right).

the onset of non-Raynaud's phenomenon SSc disease symptoms, and usually within the first 5 years.

Osteoarticular involvement

Arthralgia and arthritis are observed in more than half of the cases. Meta carpophalangeal and proximal inter phalangeal arthritis are also frequent. This joint destruction is not as severe as it is in rheumatoid arthritis but can lead to finger deformities and claw hand aspect (Figure 3). Carpal tunnel syndrome and tendon friction rubs are the consequence of the fibrosis of the tendons.

When chronic ischemic damage and fibrosis occur at the same time, an acro-osteolysis with resorption of the distal phalanx can be observed, in up to 20 percent of cases (Figure 12).

Other visceral manifestations

Pulmonary involvement: Pulmonary involvement occurs more frequently in patients with dcSSc. It mainly consists of interstitial lung disease with initial pulmonary alveoli is followed by pulmonary interstitial fibrosis. Patients may complain of dyspnea of various degrees of severity or a nonproductive cough. Some patients may be initially asymptomatic but the physical examination (basilar rales) or pulmonary function tests may reveal abnormalities. These latter tests can initially reveal an isolated reduction of diffusing capacity of the lung, before a restrictive lung syndrome with a decreased total lung capacity and forced vital capacity when lung fibrosis occurs. Frequency of lung fibrosis is estimated to be around 30 to 50 percent. Chest radiography and High-Resolution Computer Tomography (HR-CT) of the lung both show lung density or patchy air-space opacification with reticula and patchy nodular pattern (Figure 13). Interstitial infiltrates and fibrosis predominate on the lower-lobes (Figure 14).

Pulmonary arterial hypertension: Dyspnea with exertion and diminished exercise tolerance, fatigue, chest pain, and occasionally syncope may be warning signs of pulmonary arterial hypertension. In this situation, physical examination can reveal a loud pulmonary second sound (P2), left parasternal heave, lower-extremity edema, and other signs of right-sided heart failure which has a very poor prognosis. Patients with lcSSc are at high risk of developing isolated pulmonary arterial hypertension (without interstitial lung disease) whereas patients with dcSSc will develop interstitial lung disease, and later

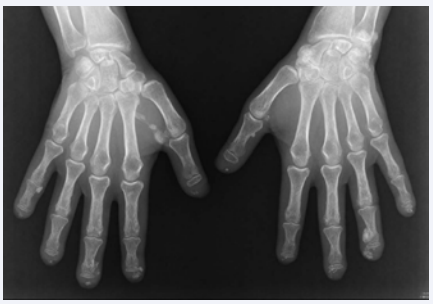

Figure 12 Hand radiology showing acro-osteolysis.

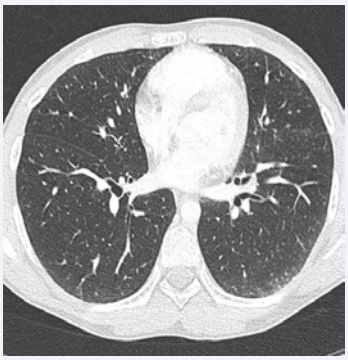

Figure 13 ThoraxHR-CT scan showing alveolitiswithground glass opacity of sub-pleural location with lobular reticulations and septal thickening.

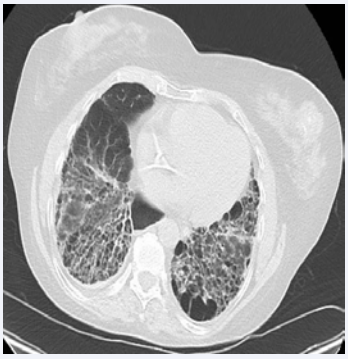

Figure 14 ThoraxHR-CT scan showing pulmonary fibrosis. Bibasal honeycomb lung pattern and air trapping sub-pleural parenchymal consolidation, traction bronchiectasis and lobular reticular opacities with moderate architectural distortion. A dilated esophagus is also visible.

pulmonary hypertension secondary to chronic lung hypoxemia. The prevalence of SSc pulmonary arterial hypertension is variable according to the screening tool: it has been found in 6 to 12 percent of cases in SSc patients when assessed by right heart catheterization and in up to 38% by echocardiography screening.

Scleroderma renal crisis is characterized by the development of severe systemic hypertension sometimes associated with hypertensive encephalopathy, acute renal failure, and micro angiopathic hemolytic anemia. A small subset (10%) of patients develop nor motensive renal crisis, mainly patients under anti-hypertensive drugs. Patients with rapidly progressive diffuse skin fibrosis, patients under steroids and patients positive for a specific SSc-autoantibody (the anti-RNA polymerase III antibody) are at greatest risk. Scleroderma renal crisis develops in approximately 5 to 12 percent of patients, with most cases occurring in dcSSc patients within the first few years. Renal failure can follow a rapidly progressive course and is associated with hematuria, proteinuria and retinal hemorrhages. Early recognition and control of hypertension with angiotensin-converting enzyme inhibitors are critical.

Gastrointestinal involvement is highly common in both forms of SSc. Atrophy of the muscularis mucosa and sub mucosal fibrosis results in varying degrees of esophageal and other gastrointestinal dysfunctions. Complaints of gastroesophageal reflux, dysphagia and heartburn in the epigastric and retrosternal regions, as well as regurgitation of gastric contents are common. They often are related to esophageal dysmotility with loss of the esophageal contractions and inferior esophageal sphincter atony, which can be explored by esophageal manometry. Esophageal disease results in reflux esophagitis, esophageal peptic strictures, and eventual development of Barrett's esophagus, a serious complication of gastroesophageal reflux disease. Gastric antral vascular ectasias (GAVE or watermelon stomach) can lead to chronic upper gastrointestinal bleeding and iron-deficiency anemia (Figure 15).

Gastric dysmotility is not rare and can lead to postprandial bloating and early satiety. Small intestinal motility may also be affected, resulting in chronic intestinal pseudo-obstruction syndrome, varying degrees of malabsorption, and bacterial overgrowth (causing episodes of diarrhea). Severe constipation may develop from colonic hypomotility. Gastrointestinal bleeding is not common, but may occur from multiple areas, from erosive esophagitis, GAVE, to diverticula in the colon. Pneumatosis cystoides intestinalis, a rare complication, can manifest as an acute abdomen. Fecal incontinence may develop due to fibrosis of the anal sphincter. Patients with lcSSc sometimes develop primary biliary cholangitis, such association being called Reynold's syndrome.

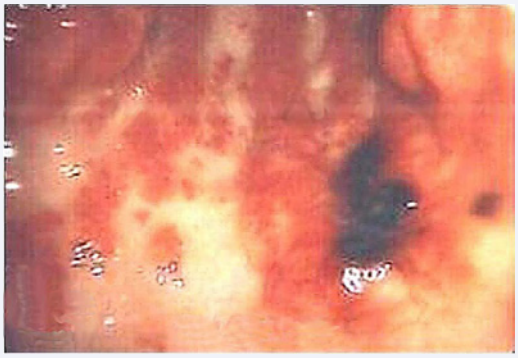

Figure 15 Endoscopic view of aGastric antral vascular ectasias (GAVE or watermelon stomach).

Although subclinical cardiac involvement is common in autopsy studies, clinical manifestations of cardiac involvement are fortunately rare, with an estimated frequency under 10 percent. Most commonly, cardiac complications are secondary to pulmonary arterial hypertension. Primary cardiac involvement mostly consists in abnormalities of the intra myocardial circulation or in rarer cases myocardial fibrosis. It can result in diastolic dysfunction, reduced left ventricular function, myocardial infarction, arrhythmias, and conduction disturbances. Pericarditis (acute or chronic) and myocarditis are also observed.

IN SUMMARY

Scleroderma can lead to severe dysfunction and failure of almost any internal organ. Most of them have been briefly described and readers should be aware that the list is not exhaustive. Besides symptoms related to organ dysfunction, the two major complaints from patients are hand disability, which has been estimated to account for 75% of patients' global disability, and facial disability. As signs of the disease are obvious on the hands and face, it becomes difficult for the patients to cope with. Hand disability has a multi factorial origin with vascular lesions, skin sclerosis, tendon retraction, bone and articular involvement, and subcutaneous calcinosis that have been detailed above. Facial manifestations should not be forgotten by physicians in patient's assessment. Each of these lesions causes pain, functional impairment, body image concerns, and psychological distress.

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