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Dariana-Elena Pătrîntașu [1], Sárközi Hédi Katalin [1,2], Eugeniu Lupușor [1], Irina Elena Vlangăr [3], Gheorghe-Marian Rotariu [4], Ionuț-Alexandru Rența [1], Anda-Nicoleta Nan [1,*] and Corina Eugenia Budin [1,5]

[1] Pneumology Department, Mures Clinical County Hospital, 540142 Targu Mures, Romania
[2] Pneumology Department, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mures, 540139 Targu Mures, Romania
[3] Cardiology Department, Elias University Emergency Hospital, 011461, Bucharest, Romania
[4] Faculty of Medicine, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mures, 540139 Targu Mures, Romania
[5] Pathophysiology Department, George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mures, 540139 Targu Mures, Romania
* Correspondence: n.anda19@yahoo.com

Abstract: Systemic sclerosis (also known as scleroderma) is a chronic fibrosing autoimmune disease with both skin and multisystem organ involvement. Scleroderma has the highest mortality among all rheumatic diseases. The pathophysiology mechanism of systemic sclerosis is a progressive self-amplifying process, which implicates the widespread microvascular damage, followed by a dysregulation of innate and adaptive immunity and inflammation, and diffuse fibrosis of the skin and visceral organs. Fibrosis of internal organs is a hint for systemic sclerosis, moreover associated with interstitial lung disease (SSc-ILD) is a complex process. We report a case of a 56 years old female, diagnosed with Systemic Sclerosis 16 years ago. The systemic and clinical manifestations, respiratory functional tests, radiological aspects and specific therapy were discussed.

Keywords: systemic sclerosis; interstitial lung disease; lung diseases; Raynaud's syndrome

1. Introduction

Systemic sclerosis (also known as scleroderma) is a chronic fibrosing autoimmune disease with both skin and multisystem organ involvement [1,2]. Scleroderma has the highest mortality among all rheumatic diseases [3]. Its pathophysiology is complex, an altered balance of the acquired and innate immune system leads to the release of several cytokines and chemokines, as well as autoantibodies, which induce the activation of fibroblasts with the formation of myofibroblasts and the formation of a rigid connective tissue [1].

Fibrosis of internal organs is a hint for systemic sclerosis, moreover associated with interstitial lung disease (SSc-ILD) is a complex process involving inflammation, alveolar epithelial damage, and activation of resident fibroblasts resulting in thickening of the lung interstitium [2,4,5].

1.1. Pathophysiology

Genetic factors likely contribute towards disease susceptibility and could explain some of the clinical heterogeneity of the disease, also environmental and occupational exposures, specifically silica, solvents, pesticides and epoxy resins have been implicated as potential causative factors [6–8].

The pathophysiology mechanism of systemic sclerosis is a progressive self-amplifying process, which implicates the widespread microvascular damage, which is believed to play a central role, followed by a dysregulation of innate and adaptive immunity and inflammation, and diffuse fibrosis of the skin and visceral organs [6,9–11].

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Most likely vascular injury (possibly initiated by viruses, autoantibodies, chemicals, or oxidative products) and dysfunction of the endothelium causes local tissue ischaemia which promotes tissue fibrosis [11]. Fibroblast to myofibroblast transition is believed to be a key event, and is driven by a number of profibrotic factors, in particular transforming growth factor-beta [6,8].

The dysregulation of the innate and adaptative immune system response plays an important role and includes the increased presence and altered functions of inflammatory cells and products in target tissues, such as the skin and lungs, together with a polymorphism in IFN-regulatory factors which confers an increased risk of SSc [1,9,12,13].

The inflammatory profibrogenic cytokines and growth factors lead to the activation of fibroblasts [1,14]. The origin of these fibroblasts has been discussed to derive from the circulation, and also from the subcutaneous layer, from transdifferentiation or from resident cells in the tissue [1]. Activated fibroblasts produce ET-1, a potent vasoconstrictor that is able to increase fibronectin synthesis in normal and SSc human skin [9,15]. These have the characteristics of myofibroblasts, which have long been regarded as the key culprit in SSc fibrosis [14,16].

Another interesting aspect of SSc is the loss of the subcutaneous adipose tissue [1,17]. Subcutaneous adipose mesenchymal stem cells and mature adipocytes are both involved in the transdifferentiation into fibroblast-like cells. The adipocytes from fibrotic locations in SSc are phenotypically different from normal adipocytes [18,19].

The progression of the pathophysiological ways implicated in the SSc are mirrored by the patient clinically features [20–22].

1.2. Diagnosis and Classification

Because there is no a single diagnostic test, the diagnosis of systemic sclerosis is usually based on clinical features, but is supported through results from targeted investigations, in consequence of which several sets of classification criteria have been developed such as 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Criteria [6,23,24].

The most widely used technique divides systemic sclerosis into subsets: limited (LcSSC) and diffuse cutaneous systemic sclerosis (DcSSc), based upon the skin involvement (Table 2) [26,27]. The term ‘CREST’ (calcinosis, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly and telangiectases) is a useful hint for some of the dominant features of systemic sclerosis, because patients with diffuse disease can also develop all of these manifestations [6].

Moreover, very early systemic sclerosis should be suspected in the presence of RP (Raynaud’s phenomenon), PF (puffy fingers), and ANA positivity (positive antinuclear antibody), which were identified as the three “red flags” that should raise suspicion [28,29].

1.3. Clinical Manifestations

1.3.1. Skin

Skin fibrosis is one of the dominant clinical features of SSc. The extent of skin fibrosis in SSc is most commonly assessed using the modified Rodnan skin score (mRSS), which measures skin thickness on a scale of 0 to 3 at 17 anatomical sites (score range 0–51). [30,31].

1.3.2. Digital Vascular Disease

The fingers are commonly affected but other sites can be involved too, including the toes and other vascular areas (e.g. lips and ears) [6]. Digital ulcers are a combination of the progressive microangiopathy and digital artery disease, commonly meet in systemic sclerosis [32,33]. Often occur on the fingertips and over the dorsal (extensor) aspects of the hands overlying the small joints. [32].

1.3.3. Cardiovascular System

In systemic sclerosis cardiovascular involvement is common and can be life threatening, because primary cardiac manifestation is often subclinical [34]. Arrhythmias are one of most severe and

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potentially fatal complications in SSc, but also an increased risk of atherosclerotic disease has been reported [28,35].

1.3.4. Respiratory Tract

Today, respiratory involvement (pulmonary fibrosis and pulmonary artery hypertension) is among the leading causes of SSc-related death [28,36]. Systemic sclerosis-associated interstitial lung disease is the end result of the interplay between fibrosis, autoimmunity, inflammation, and vascular injury [37]. Clinical symptoms occur late and are nonspecific, but when reported, dyspnoea, non-productive cough, and overwhelming fatigue are the most common symptoms [37,38]. Physical examination reveals velcrolike crackles on auscultation in addition to the cutaneous findings and pulmonary function evaluation often reveals restriction [37,40].

HRCT is the gold standard for early diagnosis of SScILD [4,39]. The most common imaging pattern on HRCT is nonspecific interstitial pneumonia, which is seen in more than 70-80% of patients with SSc-ILD [37,39,41]. It is characterised by peripheral ground-glass opacities with an apical to basal gradient, frequently accompanied by subpleural sparing. Parenchymal changes are defined by the presence of reticulation, traction bronchiectasis, and bronchiolectasis in a similar distribution [39,42]. Also, functional pulmonary testing (spirometry and Dlco), is mandatory to identify developing progressive interstitial lung disease.

1.3.5. Gastrointestinal and Renal System

Increased deposition of collagen deposition and other components of extracellular matrix lead to fibrotic changes in the upper and lower GI tract, resulting in dysmotility, malabsorption, malnutrition and dilation of the intestine [43,44]. The commonly reported symptoms of SSc includes meteorism (87%), fecal incontinence (23%) and features related to reduced esophageal motility or gastroparesis like dysphagia, heartburn and gastrointestinal reflux symptoms [6,43]. In addition to pulmonary clinical manifestations, coughing and a sore voice can occur [44,45].

Moving forward, among all possible systemic sclerosis internal organ complications, kidney involvement is frequently underestimated, because usually are attributed to other health problems [46,47]. The primary event of kidney damage is an injury to the endothelial cells, causing intimal thickening and proliferation of intralobular and arcuate arteries [47]. Typical clinical features appear with the onset of accelerated hypertension: severe headache, blurred vision and other encephalopathic symptoms. Otherwise, most patients with scleroderma renal crisis (SRC) complain of non-specific symptoms including: increased fatigue, dyspnea or just dizziness [48].

1.3.6. Musculoskeletal System

The musculoskeletal system is commonly affected in patients with systemic sclerosis [6]. For example, joint involvement can range from non-specific arthralgia and myalgia to rheumatoid arthritis (RA) [49]. Hand (finger) flexion contractures are an important cause of disability [50]. Bilateral carpal tunnel syndrome (CTS) or median neuropathy at the wrist (MNW) can be seen in patients with early disease and is sometimes the first non-Raynaud's presenting feature of systemic sclerosis [49,51].

2. Case Scenario

The presented case is from a patient admitted to the Pneumology Department of the Mures Clinical County Hospital. Informed consent was obtained from the patient. This study was conducted in accordance with the Declaration of Helsinki.

We present the case of a 56 years old female, with prolonged professional exposure (worked in vulcanization), diagnosed with Systemic Sclerosis 16 years ago (anti-Scl-70 antibodies=7.2, antinuclear antibodies=21.3 UI/ml) , with the onset of symptoms in 2003, with secondary Raynaud's syndrome, digital ulcers, recurrent pneumonia and pericarditis in 2007, respiratory failure and interstitial lung disease proggresive pattern, initially on treatment with immunosuppressive agents (

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Cyclophosphamide 100 mg/day) (stopped in December on her own initiative), later on treatment with Methotrexate 20 mg/week (stopped in June 2012 for administrative reasons). Since december 2015, treatment with endothelin receptor antagonists (Bosentan 2x125 mg/day) has been initiated, to which a PDE-5 inhibitor (Sildenafil 3x20 mg/day) has been associated since 2019, the patient being included in the National Treatment Program for patients with Arterial Hypertension Pulmonary. From 7th may 2022, antifibrotic treatment with tyrosine-kinase inhibitors was initiated (Nintedanib 150 mg 2x1/day, later 100 mg 2x1/day from 10.12.2022). The patient is also known to have viral hepatitis B (under antiviral treatment with Entecavir), L4-L5 spondylolisthesis, cervico-dorso-lumbar spondylodiscarthrosis, hepatic steatosis, reflux esophagitis, pangastric erosive and hemorrhoidal disease (upper digestive endoscopy and colonoscopy 2018). Moreover, recently she was diagnosed with ostheoporosis (T-score -3.1) and low serum levels of vitamin D, being initiated on treatment with bisphosphonate medication (ibandronic acid 3mg/day) and high doses of D3 vitamin.

Objective examination and examination of the locomotor system

Normosthenic patient, BMI 23.78 kg/m^2, face with the appearance of a "Byzantine icon", widened palpebral fissures, with deletion of nasolabial folds, decreasing mouth opening and multiplication of peribuccal folds. Indurated, hyperpigmented skin, sclerodactyly, fingers fixed in flexion, bilateral upper limb digital ulcerations, II,III,V toes, multiple stellate scars at the level of the phalanges of the upper limbs, cold, pale feet with active ulcer second toe left foot. Active mobilization accompanied by diffuse joint pain and cramping when mobilizing the knees, accentuated dorsal kyphosis, anteprojected shoulders, limitation of lateral flexion, cervical and lumbar spine pain, flattening of the lumbar lordosis, muscle contracture of upper border trapezium and bilateral dorso-lumbar paravertebral, percussive sensitivity of the spinous apophyses dorso-lumbar spine, painful limited anteflexion, crural plexus elongation positive bilaterally, Schober 10/13 cm, Lasegue positive bilaterally. Kyphotic thorax, vezicular murmur present bilaterally, bilateral basal Velcro rales, oxygen saturation 87% in ambiental air, 97% with oxygen mask 6-8 L/min. Apexian shock in the left V intercostal space on the medio-clavicular line, rhythmic heart sounds, sound II accentuated and doubled at the pulmonary area, ventricular allure 68/min, blood pressure 110/80 mmHg, palpable peripheral pulse bilaterally at the pedis artery. Microstomia, abdomen located in the xipho-pubic plane, sensitive to deep palpation in the right hypochondrium, the spleen is not palpable, the Giordano maneuver is negative bilaterally. Temporospatial oriented, symmetrical triggerable osteo tendinous reflexes, without signs of meningeal irritation, overall low muscle strength, low tactile and superficial sensitivity at the level of the affected skin.

2.1. Investigations

2.1.1. Electrocardiography

Sinus rhythm, right axis deviation, right bundle branch block (RBBB), negative T-wave in DIII, V1-V4.

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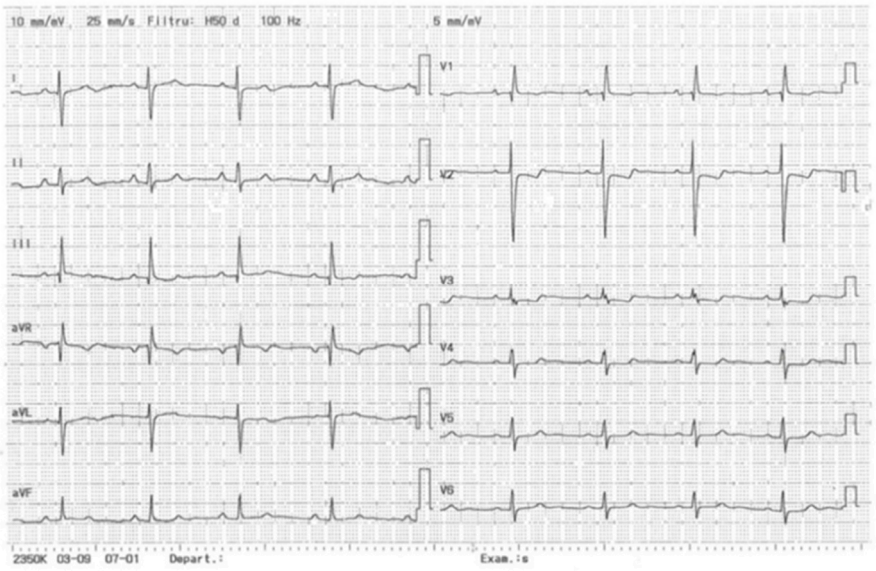

Figure 1. Electrocardiogram of the patient.

2.1.2. Minutes Walking Test

At start ventricular rate=59/min and oxygen saturation=85% in ambiental air, dyspnea (Borg scale) =2.

At stop ventricular rate 71/min, saturation=82%, dyspnea (Borg scale) =7. Total distance=50 meters (9 % of the predicted distance = 551m). The test was stopped after one minute and 13 seconds, due to marked dyspnea and the feeling of vertigo manifested by the patient.

2.1.3. Echocardiography:

MITRAL VALVE: mobile, moderate atherosclerotic changes, hemodynamically insignificant. **AORTIC VALVE:** tricuspid, mobile, moderate ATS changes, hemodynamically insignificant. **TRICUSPID VALVE:** normally inserted, flexible, mobile. **PULMONARY VALVE:** supple, mobile. **INTERATRIAL SEPTUM/INTERVENTRICULAR SEPTUM:** intact. **LEFT VENTRICLE**: efficient, without segmental and global kinetic disorders, global EF 55%, diastolic dysfunction grade I. **RIGHT CAVITIES:** RV 30/34/56 mm, hypokinetic **TAPSE** = 17 mm. **MAPSE** = 13 mm.

CONCLUSIONS: Efficient, non-dilated LV, global EF 55%, with diastolic dysfunction grd 1, minor mitral regurgitation, moderate pulmonary regurgitation. Hypokinetic RV. Severe systolic pulmonary hypertension, echocardiographic criteria showing very high probability of pulmopnary hypertension. GLPS LAX: 11.5; GLPS A4C:10.3; GLPS A2C: 13.1; AVERAGE GLPS: 11.7; Biplane FE: 55%, EDV: 72 ml, ESV 41 ml, SV 31 ml, LVCO: 2.3L/min, GLPS VD: 7.8%.

Table 1. Echocardiography of the pacient.

Dimensions	Values in mm	Normal values
RV	32	22-44
LV	36	35-60/21-40
IVS	11	6-11
Post. wall	10	6-11
LA	32	23-45
LA dimension in cm^2	15	
LA volume	-	
RA	-	
RA dimension in cm^2	16	
AOring	19	14-26

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AO asc.	23	21-34
PAring	21	10-22
PAtrunk	22	9-29
EF	55%	60%

RV: right ventricle; LV: left ventricle; IVS: interventricular septum; LA: left atrium;.RA: right atrium; AO: aortic; PA: pulmonary artery; EF: ejection fraction.

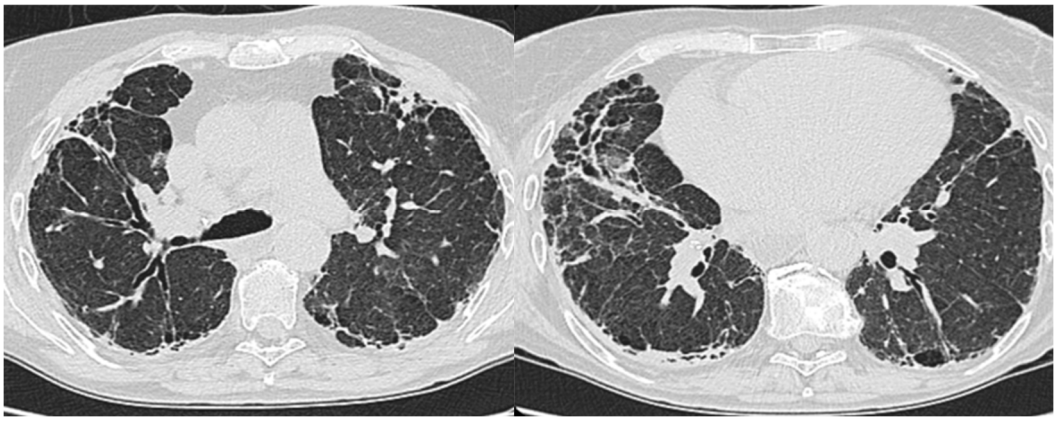
2.1.4. Bone Densitometry:

The BMD measured at Femur Neck Right is 0.601g/cm2, with a T score of -3.1.

Table 2. Densitometry evaluation.

Densitometry Trend: Total Mean				
Measured Date	**Age (years)**	**BMD (g/cm²)**	**Change vs Previous(g/cm²)**	Change vs Previous (%)
28-Oct-2022	55.4	0.693	-0.138*	-16.6*
19-June-2018	51.0	0.831	-0.031*	-3.6*
12-July-2016	49.1	0.862	-	-
Osteoporosis: YA t-score: -3.1				

2.1.5. High-Resolution Computed Tomography (october 12th 2022)



(**a**) (**b**)

Figure 2. (a,b): Computed Tomography of the Thorax.

Thyroid gland of normal appearance. Advanced fibrotic changes in both lung fields with septal thickening, architectural disorganization and traction bronchiectasis, the changes being more important at the basal level of the bilateral lower lobes. Small diffuse calcified granulomas bilaterally, without areas of pulmonary condensation. Absence of suspicious pulmonary nodules. Trachea and bronchi with free lumens. Absence of mediastinal masses. Absence of pleural fluid accumulations. Mediastinal adenopathies up to 17 mm prevascular, 16 mm pretracheal at the right, 18 mm left hilar, 15 mm right hilar, and multiple subcentimeters, some with punctate calcifications. Esophagus minimally dilated, with liquid content. Cardiomegaly, pericardial blade up to 18 mm in the right ventricle. Accentuation of dorsal kyphosis. Early degenerative changes in the dorsal spine, without suspicious lesions on the scanned bone segment. Conclusions: Pulmonary fibrosis changes with medium-advanced damage. Pericardial minimum. Esophageal stasis, more likely in the context of achalasia. Bilateral mediastinal and hilar adenopathies, some with calcifications.

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2.1.6. Spirometry

Mixed ventilatory disfunction predominantly restrictive, decreased vital capacity (VC) by 45%, decreased forced expiratory volume in one second (FEV1) by 45.4%. Normal Tiffneau index.

2.1.7. Bodypletismography

Airway resistance (RAW) and total airway resistance (Rtot) normal values, resistance-volume ratio (R-V) 83% (normal value), low total lung capacity - 67%(TLC) and Functional residual capacity (FRC) – 80%.

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Table 3. Bodypletismography.

Bodyplethysmography/ Flow-Volume			
	Pred	**Pre**	%(Pre/Pred)
R tot	0.30	0.35	116
sG tot	1.04	1.10	106
R eff	0.30	0.28	93
FRCpl	2.75	2.19	80
RV	1.87	1.55	83
TLC	5.10	3.4,	67
VC IN	3.09	1.44	47
FVC	2.99	1.87	63
FEV 1	2.54	1.46	57
FEV1%M	78.65	77.87	99
FEV1%F	78.65	77.87	99
PEF	6.32	3.54	58
FEV6		4	
MEF 75	5.54	2.57	46
MEF 50	3.63	1.74	45
MEF 25	1.47	0.55	37

2.1.8. Lung Diffusion Capacity

Verry low values of diffusing capacity of the lung for carbon monoxide (Dlco) – 25% and carbon monoxide transfer coefficient (Kco) – 41%.

Table 4. DLCO.

Diffusion SB			
	Pred	**Best**	%(Best/Pred)
DLCO_SB mmol/(min*kPa)	8.06	2.04	25
KCO_SB mmol/(min*kPa*L)	1.58	0.65	41
VA_SB (L)	4.95	3.12	63
Hb g(Hb)/dL	13.50	13.40	99
DLCO mmol/(min*kPa)	8.06	2.04	25
KCOc_SB mmol/(min*kPa*L)	1.58	0.65	41
VIN (L)		0.00	
TLC_SB (L)	5.10	3.26	34
FRC_SB (L)	2.75	2.20	90
ERV_SB (L)	0.88	0.72	91
RV_SB (L)	1.87	1.48	90
RV%TLC_SB (%)	38	46	121

Functional respiratory studies reveal a restrictive type pattern, due to pulmonary fibrotic lesions. Pulmonary interstitial damage is caused by the rheumatological pathology, progressive systemic scleroderma coexisting with the ethiological context of pulmonary arterial hypertension.

2.1.9. High-Resolution Computed Tomography (march first 2023)

Predominantly subpleural reticular lesions, with a four-cornered appearance, associated with minimal right anterobasal peribronchovascular extension. Traction bronchiectasis associated with the reticular beaches above. Subpleural areas of honey combing more accentuated in the lower half of the lung. Discrete peripheral organizing masses, especially left posterior. Fibrous bands with small associated calcifications. The pleural contour is irregularly marked, with numerous spicules on the

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contour. The esophagus is markedly dilated along its entire length, with a caliber of up to 26 mm, with regular walls, with liquid stasis in the lower half. Circumferential pericarditis in a small amount. Global cardiomegaly. The pulmonary artery cone has a caliber of 36 mm, in the context of known pulmonary hypertension. Numerous supracarinal bilateral mediastino-hilar adenopathies, some of them with small calcifications, with an inflammatory appearance. Thyroid with normal position and dimensions, inhomogeneous, micropolynodular structure. Conclusions: The CT appearance is an appearance of interstitial lung pneumopathy progressive fibrosing phenotype, examination quasi-identical to the previous CT examination. Dilated pulmonary arteries with appearance of PAH. Minimal pericarditis. Cardiomegaly. Polynodular goiter. Dorsal spondylarthrosis.

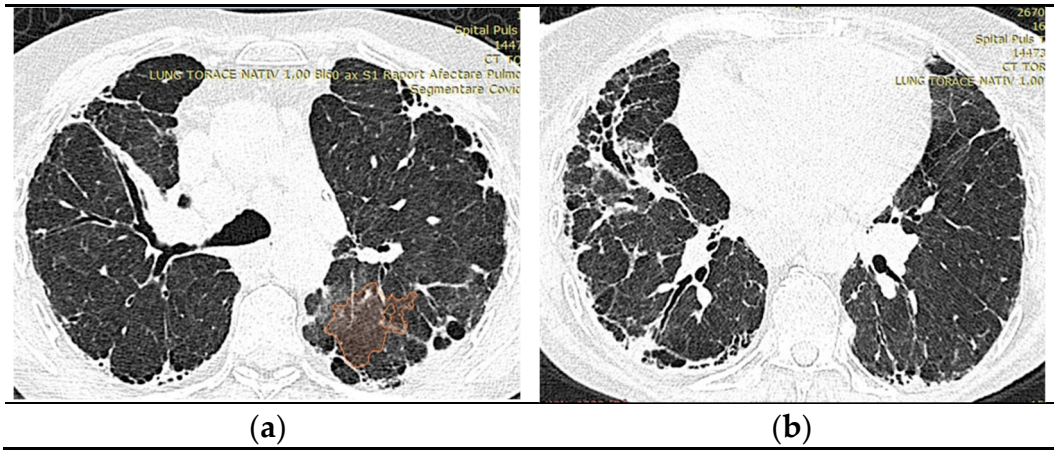

Figure 5. (a,b): Reevaluation of Lung Tomography.

Considering the underlying pathology, progressive systemic sclerosis and interstitial lung disease, the next step on the diagnostic algorithm was progressive evaluation. The restrictive pattern expressed on body plethysmography associated with a significant decrease in DLCO, the clinical deterioration of the patient and the progression of imaging lesions on HRCT led to the classification of the patient as SSC-ILD progressive phenotype.

2.2. Management of SSc

Treatment of SSc can be tough due to its rarity and heterogeneous disease manifestations [52]. Best practice often involves shared medical care and therapy should be implemented to point direclty active organ-specific complications of disease.

2.2.1. Cutaneous and Vascular Involvement

In addition to skin thickening, cutaneous disease involves the presence of calcinosis and pruritus, which is common, results as a consequence of small fiber neuropathy [53]. Immunosuppressive therapies include methotrexate, mycophenolate mofetil, with modified Rodnan skin score (mRSS) routinely used to quantify the extent of cutaneous sclerosis [52,54]. For peripheral vascular system (Raynaud's phenomenon, digital ulcers and critical ischaemia) the following therapies help reduce the frequency and severity of vascular manifestations: calcium-channel blockers, phosphodiesterase type 5 inhibitors, angiotensin II receptor blockers, endothelin receptor antagonists, prostacyclin analogue, wound care for digital ulcers and antibiotic therapy for infected ulcers [6,52].

Heart involvement:

Heart involvement is a strong prognostic factor in systemic sclerosis and may presents more frequently with diastolic (rather than systolic) dysfunction (heart failure with preserved ejection fraction) [53,55]. Current pharmacological therapies for heart failure include usual drug therapies such as calcium channel blockers for prevention and treatment of left ventricular dysfunction, ACE inhibitors, diuretics or calcium channel blockers for improvement in myocardial perfusion and anti-

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arrhythmic agents [6,52]. Regarding the inflammatory cardiac profile immunosuppressive therapy (for example corticosteroid or cyclophosphamide drugs) should be taken in consideration.

2.2.2. Scleroderma Renal Crisis

The use of ACEI to treat SRC, has been associated with a good outcome, and is mandatory for improvement in morbidity and mortality due to scleroderma renal crisis [56]. Additionally, education for those at high risk regarding a proper monitoring routine blood pressure and close communication of new symptom development (headache, dyspnea, dizziness, syncope) is strongly recommended [53].

2.2.3. Gastrointestinal Disease

The right management is based on symptoms appearance and evolution and it includes proton pump inhibitor or H2 blockers for esophageal acid reflux disease, nutritional supplementation for those with a restricted diet or malabsorption, esophageal dilatation for persisting dysphasia [52,53].

2.2.4. Interstitial Lung Disease and Pulmonary Hypertension

Excepting methotrexate, immunosuppressive treatments for cutaneous fibrosis are frequently successful for treating SSc-ILD, highlighting the similar etiology of both symptoms [57]. The recommendations are for cyclophosphamide, mycophenolate, rituximab, or tocilizumab, with priority given to mycophenolate due to its documented effectiveness for interstitial lung disease, skin, and good side effect profile [58,59]. Also, tyrosine kinase inhibitor nintedanib is authorized for use in treating progresive pulmonary fibrosis [58].

The progression of interstitial pathology in cases with scleroderma is a serious factor that impacts the prognosis of these patients. Progressive Pulmonary Fibrosis (PPF) is defined as the presence of pulmonary fibrosis, to which two of the following criteria must be added: aggravation of respiratory symptoms; progression of the disease from a functional point of view (decrease in FVC >5% predicted since the previous visit or in the last year or decrease in DLCO (corrected for Hb) >10% since the previous assessment); imaging evidence of disease progression evidenced on HRCT [60].

Cases in which, from a pneumological point of view, the presence of progression has been established, require special monitoring that requires the following investigations: repeating the functional tests and the walking test every 4-6 months or sooner if the symptomatology requires it; repeat HRCT at 1 year or less if there is another suspected diagnosis; performing angioCT if there are signs of pulmonary embolism.

All patients with SSc are at risk for developing pulmonary arterial hypertension. Phosphodiesterase 5 inhibitors (such as sildenafil and tadalafil), endothelin receptor antagonists (such as bosentan or ambrisentan), and prostacyclins are all used to attain functional New York Heart Association Class II or higher (light breathlessness) and minimal restriction when performing routine tasks [52,53].

2.2.5. Musculoskeletal Involvement

Common sites for inflammatory arthritis found in systemic sclerosis include the hands, wrists, elbows, knees, and ankles [61]. Inflammatory arthritis symptoms may benefit from the use of low-dose corticosteroids (less than 10 mg/day) [53].

3. Discussion and Conclusions

Improving the management of this potentially fatal SSc consequence requires early detection to risk stratify, monitor progression, and act when appropriate [58].

Considering HRCT the gold standard for detection of ILD, in our case the patient was examined every 6-12 month, but only 50%-66% of medical experts frequently conduct HRCT in newly diagnosed SSc patients, this demonstrates the wide diversity in global practice [40,62].

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The peak age of onset is 55–69 years and women are more commonly affected than men, with a reported ratio of between 3:1 to 8:1 [6] and while the full spectrum of SSc is seen among those with late-age onset SSc as it can be seen in Manno et al study [63], our patient, unfortunately, had an early onset of her clinical manifestations (at 36 years old), with cutaneous, pulmonary, cardiac and gastrointestinal involvement.

Moinzadeh et col., in their cohort study from Germany (2020) imply that pulmonary hypertension and cardiac involvement occurred substantially more frequently within the late-onset sample in terms of organ manifestation, which is consistent with prior publications [64]. Also, Veronika K. Jaeger et al., in the largest direct comparison of different ethnicities from EUSTAR 2004-2018 database strengthens the knowledge about the clinical and serological differences between black, asian and white people, in which asian people had higher prevalence of pulmonary hypertension and severe lung involvement [65].

Regarding our case, it is well known that since december 2015, the patient (caucasian female) has been included in the Romanian National Treatment Program for patients with Arterial Hypertension Pulmonary at age of 48 years old, with recurrent pneumonia and pericarditis since 2007.

It has been shown that late-age onset SSc was surprisingly protective against digital ischemia, early age being previously described as a risk factor for digital ulcers in systemic scleroderma [63,64]. Our case fits this description, digital ulcers involvement being present since the early onset in 2007.

The EULAR Scleroderma Trial and Research cohort revealed 6.6% of deaths from SSc that resulted from Gastrointestinal complications among elderly patients and patients with diffuse skin involvement [43,66]. The fibrosis of oral and perioral tissues, chronic inflammation, deformity of the oral cavity, and misalignment of osseous structures that result in microstomia and malocclusion of the teeth are the causes of oropharyngeal problems [43]. As a result, our patient suffered the gastrointestinal symptomatology detailed in scientific literature, including impaired mastication and deglutition, food leakage, regurgitation, and hoarseness of voice. Furthermore, approximately 50% to 90% of patients with scleroderma experience esophageal manifestations such as acid reflux that further triggers erosive esophagitis [67]. Our patient underwent an upper digestive endoscopy in response to the symptoms mentioned above, and erosive esophagitis and chronic gastritis were ultimately diagnosed. Because of this gastroenterological involvement, digestive intolerance to the initial dose of antifibrotic medication could be justified. The low dose of 200 mg per day divided into 2 doses could be tolerated without adverse effects.

Both the treatment of PAH and the treatment of esophagitis were managed in this case according to the latest European recommendations. The French practical guidelines brought updates to the ATS/ERS recommendations for the management of these comorbidities [68].

The connection between SSc and risk of osteoporotic fracture did not reach statistical significance so far, according to Chen et al. in their meta study (2019). However, patients with gastrointestinal involvement have impaired vitamin D absorption which leads to malnutrition and also thickening of the skin or mucosa in SSc patients reduces UV penetration and lowers pre-vitamin D3 production leading to overall lower bone density [69]. Outlining the points made above, our case demonstrated how malabsorption and skin thickening resulted in secondary osteoporosis, with a T score of -3.1, thus this patient is considered osteoporotic according to World Health Organization (WHO) criteria [70].

Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), the most common pulmonary symptoms of SSc, have been highlighted by clinical practice and the scientific community as the leading causes of death [71]. When compared to SSc patients without ILD, patients with SSc and ILD (SSc-ILD) had a mortality risk that was almost three times higher. Additionally, patients with Scl-70 (anti-topoisomerase I) antibodies, male sex, and African-American race have a propensity for more severe SSc-ILD and a higher chance of worsening over time [71,72]. Despite the fact that our case does not fit the gender and ethnicity requirements described above, the presence of pulmonary fibrosis and pulmonary hypertension, as well as the presence of anti-Scl-70 antibodies that are positive, place the patient at high risk for morbidity and mortality.

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Recent European guidelines for the treatment of SSC-ILD support as a consensus the effectiveness of medication with mycophenolate mofetil, cyclophosphamide and nintedanib. After identifying the progression, it is recommended to escalate the drug treatment, along with the non-pharmacological adjuvant. According to this algorithm based on modified Delphi process, the patient in the presented case received pharmacological treatment with nintedanib for ILD, as well as oxygen therapy at home. Immunomodulatory and antifibrotic therapies act mainly on the pathways related to autoimmune/inflammatory processes, respectively the pathways related to the production of fibrosis. Even if recent evidence suggests that immunomodulatory medication can also influence the appearance of fibrosis, self-sustaining pulmonary fibrosis requires an effective antifibrotic agent, and in the case of scleroderma, Nintedanib is the only antifibrotic licensed [73]. According to these recent recommendations, the patient in the presented case was initiated on antifibrotic therapy with nintedanib.

Goh et al. demonstrated that patients with SSc-ILD had a greater risk of eventual death for FVC declines of 10% or for FVC declines of 5-9% combined with a fall of 15% in Dlco [74], as indicated by our patient's repeated respiratory functional tests. Nevertheless, while DLco has been found to be the strongest predictor of HRCT-measured ILD [73], Ryerson et colab. additionally, identified that the 6 min walk test distance (6MWT) is an independent predictor of mortality [76]. Taking into consideration that 6MWT is being frequently used as an measure of exercise tolerance in patients with SSc-ILD [75], we tried to perform the test on our patient, but unfortunately we have been forced to stop the examination after only one minute and 13 seconds, with no more than 9% of the predicted distance completed, because of the exacerbation dyspnea and vertigo.

The particularity of this case consists in the association of multiple comorbidities burdened by a significant gravity. The extremely important systemic damage, the cardiovascular impact of the disease with the presence of severe PAH significantly affects the patient's quality of life. The association of Hepatitis B limits the possibility of using immunosuppressive medications and at the same time excludes the last step of treatment escalation: lung transplantation.

In conclusion, because of its severe circulatory and pulmonary dysfunction, unexpected onset and course, and wide range of clinical manifestations, SSc is an overall challenging condition. Patient demographics, SSc-specific traits such skin distribution and illness duration, serological markers, pulmonary function tests, and the degree of lung damage on HRCT are all important factors in risk risk factors for morbidity and mortality.

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Abbreviations

ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
ACEI	Angiotensin converting enzyme inhibitors
ANA positivity	positive antinuclear antibody
Ao	aortic
BMI	body mass index
BMD	body mass density
CREST	calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectases

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CTS	carpal tunnel syndrome
DcSSC	diffuse cutaneous systemic scleroderma
Dlco	diffusion capacity of the lung for carbon monoxide
EDV	End-dyastolic volume
EF	ejection fraction
ESV	End-systolic volume
FEV1	forced expiratory volume in one second
FRC	functional residual capacity
GI	gastrointestinal
GLPS	Global longitudinal peak strain
HRCT	High-resolution computed tomography
IFN	interferon
IL	interleukin
ILD	interstitial lung disease
IVS	interventricular septum
LA	left atrium
LcSSc	limited cutaneous systemic sclerosis
LV	left ventricle
LVCO	Left ventricle cavity obliteration
MAPSE	Mitral annular plane systolic excursion;
MNW	median neuropathy of the wrist
mRSS	modified Rodnan skin score
MWT	minutes walk test
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PF	puffy fingers
PDE 5 inhibitors	phosphodiesterase 5 inhibitors
PPF	Progressive Pulmonary Fibrosis
RA	rheumatoid arthritis
RA	right atrium
RAW	Airway resistance
RBBB	right bundle branch block
RP	Raynaud's phenomenon
Rtot	total airway resistance
RV	right ventricle
R-V	resistance-volume graph
SSc	systemic sclerosis
SSc ILD	systemic sclerosis associated interstitial lung disease
SRC	scleroderma renal crisis
TAPSE	Tricuspid annular plane systolic, excursion

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