SYSTEMIC SCLEROSIS AFFECTS ONLY SKIN? OTHER SYSTEM INVOLVEMENT: AN ARTICLE

G. Jyoshna¹, K.M. Jyoshna¹, K. Usha¹, Senthilvel Arunmozhishivam¹, Dr. K. Thirumala Naik²

¹- Pharm D Intern, Pharmacy Practice, Krishna Teja Pharmacy College, Tirupathi
¹- Mbbs House Surgeon, Sri Balaji Medical Collage, Hospital & Research Institute
²- Associate Professor & Clinical Preceptor, Krishna Teja Pharmacy College, Tirupathi

Abstract

Systemic sclerosis, also known as scleroderma, is a rare and complex autoimmune connective-tissue disease. Once considered an untreatable and unpredictable condition, research advancements have improved our understanding of its disease pathogenesis and clinical phenotypes and expanded our treatment armamentarium.

Early and accurate diagnosis is essential, while ongoing efforts to risk stratify patients have a central role in predicting both organ involvement and disease progression. A holistic approach is required when choosing the optimal therapeutic strategy, balancing the side-effect profile with efficacy and tailoring the treatment according to the goals ofcare of the patient.

KEYWORDS

Raynaud phenomenon, Microstomia, telangiectasias

INTRODUCTION

DEFINITIONS

Systemic sclerosis is a multi system disease, characterised by autoimmunologic processes, vascular endothelial cell injury, inflammation, and an extensive activation of fibroblasts. Skin, esophagus, lung, heart, and kidneys are the most frequently affected organs.¹⁻¹⁷

EPIDEMIOLOGY

• The age of disease onset ranges between 30 and 50 years.

• Autoimmune diseases often have a female predominance and this is the case in SSc, which has an overall female to male ratio of 3:1 or greater.

• The global SSc incidence and newly diagnosed population were estimated to be 8.64 per 100,000 person-years (1.78-23.57) and 0.67 million (0.14-1.84) people annually, respectively. Regarding prevalence, the global SSc prevalence and affected population were 18.87 per 100,000 persons (1.55-25.28) and 1.47 million (0.12-1.97) people, respectively.²³⁻²⁴
CLINICAL FEATURES OF SYSTEMIC SCLEROSIS

- SSc usually starts with a Raynaud phenomenon, which can precede the disease for many years.
- The clinical features of established SSc are diverse with severe fibrosis of the skin and all additional cutaneous manifestations.
- These include hardening of the skin, development of contractures, digital ulcerations and calcifications.
- They also reflect the multiple patterns of internal organ involvement and the consequences of progression of the underlying pathologic processes of vasculopathy, inflammation, and fibrosis. Particular consideration must be given to the hallmark complications of hypertensive scleroderma renal crisis (SC), pulmonary arterial hypertension (PAH), pulmonary fibrosis (PF), and GI dysmotility. (17-20)
A. Sclerodacty dermatogenous contractures (restricted mobility of digital joints) and salt-and-pepper hyperpigmentations and hypopigmentation.
B. Microstomia (radical furrowing around the mouth) with frenulum sclerosis
C. Skin thickening proximal of the meacarpophalangeal joints.
D. Typical scleroderma facial physiognomy with hyper-mimia, microstomia, telangiectasis and a beaked nose (17&19)

AETIOLOGY AND PATHOGENESIS

- The pathogenesis of this complex autoimmune disease involves multiple cell types (endothelial cells, epithelial cells, fibroblasts, and lymphocytic cells) interacting through a variety of mechanisms that are dependent on their microenvironment and several key mediators.

- Major facets of the disease include inflammation, vasculature, and the activation of connective tissue-producing cells.

- The clinical heterogeneity of Sc makes it likely that distinct pathogenetic mechanisms predominate in particular patients or subsets of disease. Similarly, the key pathways are not necessarily the same at different stages of SSc. Although a genetic component to the etiopathogenesis is likely and evidence supports genetic factors determining severity and susceptibility, there are also strong arguments, supporting environmental and chemical factors as triggers for the disease. (30)

**SKIN INVOLVEMENT**

Skin involvement is a cardinal feature of Sc and usually appears first in the fingers and hands. Within time, patients develop nonpitting edema of the fingers (puffy fingers), hands, and extremities, followed by an increasing induration and skin thickening (sclero-dactyly).
The abnormal deposition of cutaneous and/or subcutaneous calcium (calcinosis cutis), usually occurs over pressure points (acral, joints) in a period of time.

Digital ulcers are associated with strong, local pain and a major impact on quality of life regarding all-day functions (eg, dressing, eating). Other complications include critical digital ischemia, paronychia, infections, gangrene, osteomyelitis, and finger pulp loss or amputation.

CARDIOPULMONARY MANIFESTATIONS

There are different ways that the cardiopulmonary system may be involved, most often appearing as fibrosis and PAH.

Dyspnea, arrhythmia\(^{(1-20)}\)

GI INVOLVEMENT

GI involvement is the most common internal organ involvement in patients suffering from both limited and diffuse SSc (>60%). Many parts of the GI tract may be impaired, affecting motility, digestion, absorption, and excretion.

Esophageal involvement includes symptoms like dysphagia, heartburn resulting from reflux, nau-sea, and/or vomiting, esophagitis.

Possible gastric manifestations include atrophy of mucous membrane-associated ulcerations and delayed gastric emptying.

KIDNEY INVOLVEMENT

SRC appears in 5% to 10% of SSc patients, and may cause an abrupt onset of significant systemic hypertension (>140/90 mm Hg, or a rise in systolic/diastolic blood pressure 230/220 mm Hg), together with an increase in serum creatinine, proteinuria, hematuria, thrombocytopenia, or hemolysis followed by an acute renal failure.\(^{(1-20)}\)

End-organ damage can result in encephalopathy with generalized seizures or flash pulmonary edema.

MUSCULOSKELETAL SYSTEM

Musculoskeletal (MSK) involvement of the hands is a significant source of morbidity, impacting on quality of life in patients with systemic sclerosis.

chronic joint pain, inflammation and swelling in muscles and joints Arthralgia Synovitis Muscle weakness are the ailments noted

VASCULAR SYSTEM

Raynaud phenomenon due to decreased blood flow to extremities

SSc causes noninflammatory macrovascular and microvascular changes with dramatic and possibly occlusive formation of a thickened neointima.

It involves vascular disease involves vasculopathy with luminal occlusion, thrombosis, and vasospasm\(^{(1-20)}\)
### RECOMMENDED DIAGNOSTIC PROCEDURES

<table>
<thead>
<tr>
<th>System</th>
<th>Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular system</strong></td>
<td></td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>- Coldness provocation</td>
</tr>
<tr>
<td></td>
<td>- Nailfold capillaroscopy</td>
</tr>
<tr>
<td></td>
<td>- Antinuclear antibody levels</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>- Clinical assessment regarding puffy fingers, telangiectasia, mechanic hands, hypopigmentation, digital ulcerations, dermatogenous contractures</td>
</tr>
<tr>
<td></td>
<td>- Modified Rodan skin score</td>
</tr>
<tr>
<td></td>
<td>- 20-MHz ultrasonography</td>
</tr>
<tr>
<td></td>
<td>- Radiography (X-ray, MRI, CT)</td>
</tr>
<tr>
<td>Calcinosis cutis</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal system</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>- Clinical assessment regarding fist closure deficiency, joint contractures, tendon friction rub, muscle weakness</td>
</tr>
<tr>
<td>Synovitis</td>
<td>- Laboratory parameters: erythrocyte sedimentation rate, rheumatoid factor, antinuclear autoantibodies</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>- Creatine kinase (greater than threefold?)</td>
</tr>
<tr>
<td></td>
<td>- MRI, electromyography</td>
</tr>
<tr>
<td></td>
<td>- Muscle biopsy</td>
</tr>
<tr>
<td><strong>GI tract</strong></td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>- Gastro-/esophageal endoscopy</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>- Esophageal scintigraphy, esophagus manometry</td>
</tr>
<tr>
<td>Gastric antral vascular ectasia</td>
<td>- Gastro-/esophageal endoscopy with laser coagulation, if necessary</td>
</tr>
<tr>
<td>Diarrhea, obstipation</td>
<td>- Colonoscopy</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>- Lung function test (carbon monoxide transfer factor corrected for hemoglobin [TLCOc] single breath (SB), total lung capacity [TLC], forced vital capacity [FVC])</td>
</tr>
<tr>
<td></td>
<td>- Radiography (X-ray or high resolution CT)</td>
</tr>
<tr>
<td></td>
<td>- Bronchialveolar lavage (BAL) (optional)</td>
</tr>
<tr>
<td><strong>Cardiac system</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea, arrhythmia</td>
<td>- Electrocardiography (conduction blocks?)</td>
</tr>
<tr>
<td></td>
<td>- Echocardiography (mean pulmonary artery pressure, diastolic dysfunction?, ventricular ejection fraction)</td>
</tr>
<tr>
<td></td>
<td>- (Spiro-)Ergometry</td>
</tr>
<tr>
<td></td>
<td>- 24-Hour blood pressure controls</td>
</tr>
<tr>
<td></td>
<td>- Right-heart catheterization</td>
</tr>
<tr>
<td></td>
<td>- Cardiac MRI</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
</tr>
<tr>
<td>Renal function failure</td>
<td>- Regular blood pressure controls (&gt;140/90 mm Hg)</td>
</tr>
<tr>
<td></td>
<td>- Ultrasonography</td>
</tr>
<tr>
<td></td>
<td>- Serum levels of creatinine, urine analyses (protein, albuminuria, microelectrolysis)</td>
</tr>
</tbody>
</table>

### TREATMENT IN SYSTEMIC SCLEROSIS

#### VASULOPATHY
- Raynaud phenomenom
- Consistent warm keeping, paraffin-bath, patient education
- Calcium channel blockers (eg, nifedipine) by mouth
- Angiotensin receptor antagonists
- Alternatives: selective serotonin reuptake inhibitors (SSRIs), a-blockers, sympathectomy with or without botulinum toxin injection
- Digital ulcers
- Prostacyclin (eg, iloprost) IV
- Endothelin receptor blockade (eg, bosentan by mouth)
- Phosphodiesterase Type 5 inhibitors (off-label)
- Wound dressing (hydrocolloid membrane, Mepilex)

#### MUSCULOSKELETAL SYSTEM
- Synovitis/myositis
- Methotrexate (by mouth, IM)
- Rituximab (off-label) (28)

#### GI SYSTEM
- Reflux Proton pump inhibitors, prokinetics
- Dysphagia
- H.-receptor antagonists
- Diarrhea, obstipation. Change habit of eating, parenteral nutrition
- Antibiotics (eg, ciprofloxacin) Symptomatic management with antidiarreal agents or laxatives
**RESPIRATORY SYSTEM**

- Dyspnea
- Oxygen
- Alveolitis / lung fibrosis
- Cyclophosphamide IV
- Mycophenolate mofetil by mouth (used as an alternative or after cyclophosphamide)
- Glucocorticoids (short dated, if necessary)

**CARDIAC SYSTEM**

*Pulmonary arterial hypertension*
- Endothelin receptor blockade (eg, bosentan by mouth, macitentan)
- Inhaled iloprost
- Phosphodiesterase Type 5 inhibitors (eg, sildenafil by mouth, tadalafil)
- Epoprostenol by mouth
- Combination of different agents

*Diastolic heart failure*

- Diuretics
- Calcium channel inhibitors

**RENAL SYSTEM**

- Scleroderma renal crisis
- Calcium channel inhibitors
- Angiotensin-converting enzyme-Hemmer (high-dosed)\(^{(28)}\)

**MAIN REFERENCES**

Reference

17. Published online 2016 Jul 23. doi: 10.5301/jsrd.5000209
18. Global, regional, and national incidence and prevalence of systemic sclerosis
19. Jingru Tian 1, Shuntong Kang 2, Dingyao Zhang
20. 3, Yaqing Huang 4, Ming Zhao 5, Xianhua Gui 6, Xu Yao 7, Qianjin Lu 8
21. Affiliations expand
22. PMID: 36804224 DOI: 10.1016/j.clim.2023.109267