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A Comprehensive Review of Systemic Sclerosis: Diagnosis, Clinical Features and Management Strategies

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Abstract

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis of the skin and internal organs, along with vasculopathy. It is associated with significant morbidity and mortality, particularly due to pulmonary and renal complications. Early diagnosis is challenging, but crucial, as severe internal organ involvement can occur within three years of disease onset. SSc is categorized into subsets, such as diffuse and limited cutaneous forms with varying degrees of skin and organ involvement. Specific autoantibodies are critical for diagnosing and predicting disease severity and understanding these serological profiles aids in personalized treatment decisions. Management focuses on addressing specific manifestations like Raynaud's phenomenon, skin fibrosis, pulmonary involvement, and gastrointestinal issues with treatment strategies tailored to the disease's stage and organ involvement. Despite advances in treatment, SSc remains a challenging disease requiring ongoing vigilance for early detection and intervention.

Purpose

The purpose of this article is to provide a comprehensive overview of systemic sclerosis, focusing on its diagnostic criteria, clinical features and management strategies. It aims to highlight the importance of early detection, particularly in the context of skin and organ involvement and the role of serological markers in guiding diagnosis and treatment. Ultimately, the goal is to improve awareness and understanding of SSc among healthcare professionals, particularly dermatologists, to enhance early diagnosis and optimize patient outcomes.

Materials and Methods

Our review is based on an analysis of material collected in 'Pubmed', 'Google Scholar' and other scientific articles using the keywords: systemic sclerosis, antinuclear antibodies, Raynaud's phenomenon, pulmonary arterial hypertension.

Keywords: systemic sclerosis, antinuclear antibodies, Raynaud's phenomenon, pulmonary arterial hypertension

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis of the skin and internal organs, along with vasculopathy. It belongs to a larger group of fibrosing skin diseases, which vary from localized scleroderma with a few small fibrotic plaques to the widespread involvement seen in systemic sclerosis [1]. Despite the low prevalence of SSc, it poses a significant disease burden and has the highest mortality rate among rheumatic diseases [2].

The pathogenesis remains incompletely understood, but fibrosis development follows similar pathophysiological events across different fibrosing conditions. While the clinical features of advanced systemic sclerosis are distinctive and easy to diagnose, early-stage disease is often overlooked, making the condition potentially more common than recognized.

The disease typically begins with Raynaud's phenomenon, followed by skin hardening in the extremities and face, digital ulcerations, and potentially necrosis of the fingertips. Other symptoms include severe pruritus, extensive calcifications, and telangiectasias. It is often associated with severe pulmonary and renal complications, while gastrointestinal symptoms are present in most patients. Musculoskeletal involvement is common, and cardiac disease, although frequently overlooked, may be more prevalent than typically thought [3,4].

Diagnosis and Classification

The earliest signs of systemic sclerosis often include Raynaud’s phenomenon and fatigue, which, while common, are non-specific and can have various alternative causes. As many of the initial manifestations are cutaneous, dermatologists are crucial in identifying early disease, assessing the risk of progression, and detecting signs of systemic involvement. Recognizing these early presentations can significantly influence long-term outcomes, underlining the importance of ongoing education and involvement in disease management.

The diagnosis of SSc is based on clinical findings, autoantibody profiles, and additional specific investigations. Over time, the classification and diagnostic criteria for SSc have evolved with the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) introducing a more comprehensive set of criteria [5]. These updated guidelines incorporate a wide range of clinical features, vascular, serologic and imaging findings,

and a score of 9 or higher is required for an SSc diagnosis. These revised criteria have improved sensitivity for detecting early-stage SSc, which is vital for initiating disease-modifying treatments that can alter disease outcomes (Table 1).

Table 1. Classification criteria for systemic sclerosis as per the 2013 ACR/EULAR guidelines [5]

Main criteria	Additional criteria	Weighting
Sclerosis of the hands extending proximal to the metacarpophalangeal joint (sufficient criterion)		9
Sclerosis of the fingers (only count higher score)	Puffy fingers Sclerodactyly (between MCPJ and PIPJ)	2 4
Fingertip lesions (only count higher score)	Digital ulcers Fingertip pitting scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary involvement (maximum score of 2)	PAH ILD	2 2
Raynaud's phenomenon		3
SSc-typical autoantibodies (maximum of 3 points)	Anti-centromere Anti-topoisomerase I Anti-RNA polymerase III	3 3 3
MCPJ, metacarpophalangeal joint(s); *PIPJ*, proximal interphalangeal joint; *PAH*, pulmonary arterial hypertension; *ILD*, interstitial lung disease. The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 are classified as having definite SSc.		

It is important to note that severe internal organ involvement often occurs within three years of SSc onset with irreversible manifestations sometimes emerging before patients meet the ACR diagnostic criteria [6-8]. This has led to the development of the very early diagnosis of systemic sclerosis (VEDOSS) project, which identifies key early features – such

as Raynaud's phenomenon, puffy fingers, and positive antinuclear antibodies (ANA) – that are predictive of progression to established SSc. Studies show that patients with puffy fingers and disease-specific autoantibodies have a 94% probability of meeting diagnostic criteria within 5 years, emphasizing the importance of early detection. Efforts have also focused on identifying patients with Raynaud's phenomenon who are at the greatest risk for developing SSc, further underscoring the role of dermatologists in early diagnosis.

Serological Profile

Autoantibodies targeting specific nuclear antigens are a key feature of systemic sclerosis with antinuclear antibodies (ANA) detected in up to 95% of patients [9]. In a recent study [1], 86.6% of ANA-positive patients had antibodies specific to SSc, targeting five major antigens: centromere, topoisomerase-1, RNA polymerase III, exosomal ribonuclear protein (PM/Scl) and uridine-rich small nuclear ribonuclear protein (U1-snRNP). These SSc-specific antibodies are usually mutually exclusive, although rare overlaps can occur. While ANA positivity is common, identifying more specific SSc-related autoantibodies is essential for assessing organ involvement and disease severity [10-12].

Certain autoantibodies are associated with specific clinical features (Table 2) [1,13,14]. For instance, anti-TOPO I antibodies are linked to severe skin and internal organ fibrosis, as well as a higher risk of renal damage. ACA antibodies are associated with limited skin fibrosis, pulmonary hypertension, and gastrointestinal involvement. Anti-RNAP III antibodies are connected to rapidly progressing skin thickening, renal crisis, and an increased risk of cancer. Anti-U3 and anti-U11/U12 RNP antibodies indicate severe lung disease, while anti-U1 snRNP antibodies are linked to muscle and joint inflammation. Other antibodies, such as anti-PM/Scl and anti-Ku, are associated with muscle and joint involvement, as well as overlap disease.

Table 2. Autoantibodies associated with systemic sclerosis and their clinical correlates [1, 14]

	Cutaneous subtype	Clinical correlates
Anti-centromere (ACA)	Limited cutaneous systemic sclerosis	Pulmonary arterial hypertension
Anti-topoisomerase 1 (Scl-70)	Diffuse cutaneous systemic sclerosis	Progressive interstitial lung disease, renal damage
Anti-RNA polymerase III (anti-RNAP III)	Diffuse cutaneous systemic sclerosis	Renal crisis and malignancy
Anti-U1 ribonucleoprotein (anti-ribonucleoprotein)	Limited cutaneous systemic sclerosis	Muscle and joint involvement

Anti-U3 ribonucleoprotein (anti-fibrillarin)	Diffuse cutaneous systemic sclerosis	Pulmonary arterial hypertension and myositis
Anti-PM/Scl	Limited cutaneous systemic sclerosis	Muscle and joint involvement

These specific autoantibodies play a vital role in diagnosing SSc, predicting organ involvement, and determining disease prognosis. Early detection of these antibodies can help guide treatment decisions, such as considering immunosuppressive therapy to prevent organ damage. Combining serologic testing with an assessment of skin involvement is the most effective way to predict patient outcomes in SSc.

Clinical Subsets of the Disease

Systemic sclerosis is classified into several subsets, each with distinct clinical characteristics [13]:

Diffuse cutaneous systemic sclerosis (dcSSc) involves skin thickening on the trunk and proximal limbs – above the elbows and knees. It is associated with severe internal organ fibrosis, including the lungs, kidneys, and heart, and is characterized by an aggressive disease course with a poor prognosis.

Limited cutaneous systemic sclerosis (lcSSc) is primarily marked by fibrosis in the acral regions – distal to the elbows and knees. Internal organ involvement tends to occur later in the disease. However, patients with lcSSc have a higher risk of developing pulmonary arterial hypertension and gastrointestinal tract fibrosis. The "CREST syndrome" (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) and "systemic sclerosis sine scleroderma"(a very rare subset characterized by the total or partial absence of cutaneous manifestations of systemic sclerosis with the occurrence of internal organ involvement and serologic abnormalities [15]) are now recognized as part of the lcSSc spectrum.

SSc overlap syndromes present with symptoms of SSc in combination with clinical features of other connective tissue diseases, such as polymyositis, dermatomyositis, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus (SLE). These overlap syndromes generally resemble lcSSc, but with a higher incidence of myositis and arthritis compared to lcSSc or dcSSc.

Skin Involvement

There is significant variability in the extent of skin involvement in systemic sclerosis, both between patients and over time within the same patient [16]. Skin fibrosis usually begins in

the fingers and toes and spreads proximally. In the early stages, the fingers swell due to microvascular changes and inflammation, but as the disease progresses, excessive collagen deposition causes the skin to thicken and restrict joint movement, leading to contractures. In later stages, the skin may become tight, stiff and even atrophic [14].

At the disease's onset, particularly in diffuse SSc, patients may experience swollen fingers ("puffy hands"), which later develop into more severe skin changes like sclerodactyly, perioral furrowing, microstomia (oral aperture less than 4.5 cm) and stiffness in the face [17]. Sclerodactyly, or skin thickening on the fingers or toes, usually begins with swollen fingers that later become more spindle-shaped due to skin contraction. This condition is part of the diagnostic criteria for SSc. Skin tightening around the mouth can cause restricted mouth opening, affecting speech and eating. The skin on the face can also become tight, leading to a beaked nose, difficulty opening the eyes and a reduced range of facial expressions [18]. Reduced saliva and tear production, often linked to mouth and eye dryness, can result in dental problems and weight loss [19]. Other symptoms may include hair loss, reduced sweating, skin pigmentation changes and severe pruritus. As the disease progresses, skin fibrosis in the trunk and upper limbs often diminishes, while internal organ involvement may worsen [1]. About 15–25% of SSc patients develop active digital ulcers (DUs) and around 35% have experienced them at some point, though this varies across studies. Ulcers on the fingertips are usually caused by ischemia, while those on the joints result from a combination of poor perfusion, stretched skin and trauma. DUs can become infected, leading to complications like osteomyelitis or gangrene [20].

Calcinosis cutis, characterized by subcutaneous calcium deposits, can occur in all forms of SSc, typically on the acral parts of the body and may cause pain and erosion [21].

Raynaud’s phenomenon (RP) is present in more than 90% patients with systemic sclerosis [5], typically affecting the fingers and less frequently the toes, ears, tongue, nose and nipples. It is characterized by a triphasic colour change in the affected areas: pallor (due to vasospasm), followed by cyanosis (from blood sequestration and deoxygenation) and finally erythema (from post-ischemic hyperemia) [22]. RP is often triggered by cold exposure, though emotional stress can also provoke symptoms. In SSc, RP is a persistent issue with symptoms often present throughout most of the year. Numbness, tingling and pain may also accompany the color changes [23]. The progression of RP to other SSc symptoms can vary depending on the disease subtype with the transition taking months in diffuse cutaneous SSc and years in

limited cutaneous SSc. The presence of RP, along with other clinical signs like puffy fingers or positive ANA, can indicate the early stages of SSc. Furthermore, abnormalities in nailfold capillaries and the detection of specific autoantibodies are important predictors of the progression from RP to full-blown SSc [24].

Capillaroscopy, including high-resolution nailfold videocapillaroscopy, is vital for evaluating capillary changes in SSc with characteristic abnormalities such as enlarged capillaries, capillary loss and microhemorrhages. This test helps differentiate primary Raynaud's phenomenon (RP) from SSc. [25]

Skeletomuscular Involvement

Musculoskeletal involvement in systemic sclerosis is common and can manifest in various ways, often complicating the clinical picture. Patients frequently experience arthralgia and musculoskeletal pain, which may eventually lead to secondary fibromyalgia. Tendon friction rubs, characterized by a crepitus felt as the tendon moves within its sheath, are a key indicator of an inflammatory and progressive form of the disease, especially in patients with diffuse cutaneous SSc. Muscle weakness and elevated serum creatine kinase levels can signal an overlap with myositis, which is often seen in SSc patients [26]. Inflammatory arthritis affects up to 10% of individuals with SSc and may raise suspicion for an overlap with rheumatoid arthritis [1]. While joint pain and stiffness are common, some patients may also develop erosive arthritis. The presence of skin fibrosis or subcutaneous edema can complicate the assessment of joint effusion and range of motion. Early identification and management of musculoskeletal involvement are crucial, as they can significantly impact a patient's quality of life and disease progression.

Cardiac Involvement

Cardiac involvement in systemic sclerosis is a significant cause of morbidity and mortality, but there is no standardized definition for its presentation. The disease is linked to a range of severe cardiac abnormalities, including myocarditis, congestive heart failure, arrhythmias, asymptomatic focal fibrosis and impaired ventricular relaxation [14]. These cardiac issues contribute to a substantial portion of SSc-related deaths. Even in the absence of symptoms, it is recommended that patients with SSc undergo routine evaluations using electrocardiograms and echocardiograms. Cardiac MRI should be considered when these tests indicate potential cardiac involvement [27]. For patients at risk of malignant arrhythmias, tools like Holter monitoring and implantable loop recorders may be necessary [28]. Common

cardiac manifestations of SSc include heart failure, pericardial effusions, arrhythmias and in rare cases, valve sclerosis. These issues are particularly prevalent in older patients and those with anti-topoisomerase antibodies. Symptoms of cardiac involvement include heart failure, shortness of breath, reduced exercise tolerance, chest pain, palpitations, syncope, fatigue, dizziness and peripheral edema.

Gastrointestinal Involvement

Gastrointestinal (GI) involvement occurs in at least 90% of patients with systemic sclerosis with a wide range of manifestations that can appear at any stage of the disease [29]. Esophageal issues are particularly common, often presenting as reflux disease, which may or may not be accompanied by esophagitis. Esophagitis can be asymptomatic and an endoscopic examination is necessary for diagnosis [30]. Dysphagia, or difficulty swallowing, is often a result of esophageal motility problems. Gastric antral vascular ectasia is a potentially life-threatening complication that can cause slow or rapid blood loss, making upper endoscopy critical for patients with anemia [31]. Delayed gastric emptying is another issue, leading to abdominal bloating and discomfort, especially after meals. Lower GI involvement affects up to 50% of patients, contributing to higher rates of morbidity and mortality [32]. Symptoms include small intestinal bacterial overgrowth, malabsorption, constipation, diarrhea, recurrent pseudo-obstruction and fecal incontinence [33,34]. Intestinal pseudo-obstruction, seen in 4% to 10% of patients, is a serious condition that arises from delayed colonic transit, where the intestinal contents are unable to move forward despite the absence of a mechanical obstruction [35-38]. This painful and often recurrent condition can sometimes be life-threatening [39]. Anorectal issues, including fecal incontinence, affect 22% to 77% of patients with rectal prolapse also occurring, causing a bulging sensation and chronic stool leakage [40]. In severe cases, total parenteral nutrition may be required. Along with general malnutrition, patients may also experience micronutrient deficiencies, which need to be assessed through specific testing [41,42]. In patients with long-standing disease (over 10 years), almost all will develop upper GI issues, including Barrett's esophagus as a late result of reflux disease and mucosal telangiectasia, which can be a source of hidden intestinal bleeding [1].

Pulmonary Involvement

Interstitial lung disease (ILD) affects up to 65% of patients with systemic sclerosis, presenting primarily as a bibasilar pattern, often linked to non-specific interstitial pneumonitis [43].

High-resolution CT (HRCT) is more sensitive than lung function tests in detecting ILD, though lung function testing (spirometry, plethysmography and DLCO) remains important for monitoring disease progression [44]. Some may have stable ILD, while others experience varying rates of progression with rapid progression being more common in certain groups, including males, African Americans and patients with the Scl70 autoantibody [45,46].

Non-specific interstitial pneumonia is the most common histological pattern in SSc with usual interstitial pneumonia present in 10–25% of cases [47,48]. HRCT can detect early ILD and identify other systemic sclerosis features, like a dilated pulmonary artery and comorbidities, such as pulmonary malignancy [49]. Pulmonary function tests are critical for monitoring progression, although variations and external factors, such as fibrosis or muscle weakness, can affect the results. Progressive ILD is defined by worsening symptoms, radiological progression and physiological decline within a year [50]. Experienced thoracic radiologists play a key role in identifying subtle ILD progression on HRCT. While invasive procedures like broncho-alveolar lavage or lung biopsy are typically reserved for uncertain diagnoses, they can be useful in complex cases.

Pulmonary arterial hypertension is a serious complication of SSc with a 3-year mortality rate between 21% and 48% [51,52]. It is more common in patients with anti-centromere antibodies, extensive telangiectasias and longer disease duration. Emerging evidence suggests a higher prevalence of PAH in patients with Th/To autoantibodies [53]. SSc-associated PAH has a poorer prognosis compared to idiopathic PAH, even with similar hemodynamic profiles [54].

Right-heart catheterization is the gold standard for diagnosing PAH, though echocardiography and PFTs can help with screening. Algorithms like the DETECT and Australian Scleroderma Interest Group methods aid in determining the need for right-heart catheterization [55-57].

Renal Involvement

Chronic renal involvement in systemic sclerosis is linked to progressive obliterative vasculopathy, while acute renal crisis (SRC) is a severe, potentially fatal complication. SRC typically affects patients with the diffuse form of SSc within the first four years of disease and is associated with anti-RNA polymerase III antibodies, found in about one-third of cases [58].

Renal crisis prevalence ranges from 1% to 14% with higher rates in the USA, UK and Australia [59]. It is characterized by rapid renal failure and malignant hypertension, which can lead to end-stage renal disease if left untreated. Without prompt intervention, renal failure can progress rapidly within weeks of the first symptoms [60]. However, the introduction of ACE inhibitors has significantly reduced 1-year mortality rates [61].

Risk factors for renal crisis include diffuse cutaneous SSc, a quick disease progression, African American race, pericardial effusion, tendon friction rubs, high-dose corticosteroid use (greater than 15 mg/day) and RNA polymerase III antibodies [62]. Microangiopathic hemolytic anemia and thrombocytopenia are common, so blood smear analysis is essential. Kidney biopsy is reserved for cases of diagnostic uncertainty.

Some patients with renal crisis may be normotensive, which signals poor cardiovascular reserve and a poorer prognosis. Timely blood pressure monitoring is critical to managing this life-threatening complication [63].

Treatment

To effectively treat systemic sclerosis, it's essential to evaluate the disease subtype, organ involvement and level of activity. Recent pharmacological advancements have greatly enhanced patient outcomes by addressing specific manifestations of the disease. Treatment guidelines consider the diverse healthcare systems across Europe with recommendations shaped by factors such as hospital protocols, outpatient services and available resources.

Raynaud's Phenomenon and Digital Ulcers

Preventing cold exposure is crucial in managing Raynaud's phenomenon with heated gloves and physical therapy often recommended. Calcium channel blockers like nifedipine or amlodipine are first-line treatments and PDE-5 inhibitors can also help in some cases.

For more severe cases iloprost or digital sympathectomy may be used. Cessation of smoking and avoidance of beta-blockers are important for symptom control. Digital ulcers should be treated with antibiotics, vasodilators to improve circulation and appropriate pain management [64]. Bosentan may help prevent new ulcers, while PDE-5 inhibitors can promote healing of existing ones [65].

Skin Fibrosis

Treatment for skin fibrosis is based on the disease's phase and activity level. In mild cases, general measures such as skin protection, moisturizing and physiotherapy are often sufficient. UVA therapy may help in the early stages and photopheresis shows promise for more advanced disease [66-68]. For progressive fibrosis, methotrexate and MMF are the most effective therapies with cyclophosphamide considered if these options fail [69,70]. Glucocorticoids should be avoided due to their association with renal crisis [58].

Calcinosis Cutis and Telangiectasia

When calcinosis cutis leads to symptoms or circulatory issues, surgical excision or carbon dioxide laser treatment may be needed [71]. Telangiectasia can be managed with laser therapy, although cosmetics are commonly used to cover affected areas [72].

Pulmonary Involvement

For lung fibrosis, early treatment with cyclophosphamide is vital, followed by immunosuppression in cases of disease progression [73]. Autologous stem cell transplantation is a promising option for some patients but comes with higher risks in the first year [74]. Pulmonary arterial hypertension should be managed by specialists with regular echocardiography to monitor progress.

Gastrointestinal and Renal Involvement

Gastroesophageal reflux disease is commonly treated with proton pump inhibitors with additional options like prokinetics for dysphagia [69]. For gastrointestinal infections or severe malnutrition, antimicrobial therapy or parenteral nutrition may be necessary. Prompt detection of scleroderma renal crisis is essential for optimal outcomes with ACE inhibitors being the primary treatment. Other antihypertensive medications may be used for managing resistant hypertension.

This comprehensive guideline addresses the various manifestations of SSc and underscores the importance of individualized care, ensuring that each patient receives the most effective treatment tailored to their specific needs.

Summary

Systemic sclerosis is a rare autoimmune disease marked by skin fibrosis, internal organ involvement and vasculopathy. Early symptoms, such as Raynaud’s phenomenon and skin hardening are often overlooked but crucial for early diagnosis. The disease is diagnosed using clinical findings, autoantibody profiles and updated criteria with early detection improving outcomes.

SSc has several forms, including diffuse and limited with varied skin and organ involvement. Common complications include cardiac issues, gastrointestinal problems, pulmonary fibrosis and renal crises. Treatment focuses on managing symptoms and preventing organ damage with options like calcium channel blockers for Raynaud's, immunosuppressants for skin fibrosis and ACE inhibitors for renal crises. Early diagnosis and individualized care are essential for better patient outcomes.

Disclosure

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