Distinctive Clinical Features Of Patients With Systemic Sclerosis

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ABSTRACT

Systemic sclerosis is a rare, chronic, multisystem autoimmune connective tissue disease in which microvascular injury, immune dysregulation, and progressive fibrosis combine to produce one of the most heterogeneous clinical phenotypes in modern rheumatology. The disease may begin insidiously with Raynaud's phenomenon, puffy fingers, fatigue, reflux symptoms, or subtle nailfold capillary abnormalities long before a fully classifiable syndrome emerges, yet it can subsequently evolve into a condition marked by skin thickening, digital ischemia, gastrointestinal dysmotility, interstitial lung disease, pulmonary vascular disease, cardiac involvement, renal crisis, musculoskeletal dysfunction, and major impairment in quality of life and survival. The present narrative review aims to synthesize contemporary evidence on the distinctive clinical manifestations of systemic sclerosis, emphasizing the temporal evolution of symptoms, phenotype-based stratification, and the diagnostic significance of early vascular and cutaneous clues. Particular attention is given to the clinical contrast between limited cutaneous and diffuse cutaneous disease, the importance of systemic sclerosis-specific autoantibodies as markers of organ risk rather than mere laboratory labels, and the relevance of very early diagnosis frameworks in patients who present with Raynaud's phenomenon before overt fibrosis develops. The review also examines the major organ-specific manifestations that define disease burden, including esophageal dysfunction, malabsorption, pulmonary fibrosis, pulmonary arterial hypertension, myocarditis-like and arrhythmic phenotypes, and scleroderma renal crisis, together with overlap syndromes and systemic sclerosis sine scleroderma. By integrating classification criteria, cohort data, and recent guideline-based approaches to assessment, this paper argues that the clinical identity of systemic sclerosis is best understood not as a static syndrome but as a dynamic phenotype in which the sequence, clustering, and severity of manifestations determine prognosis and guide surveillance. Recognition of the disease's characteristic clinical signatures—especially persistent Raynaud's phenomenon with abnormal capillaroscopy, puffy fingers, digital lesions, telangiectasia, evolving sclerodactyly, early reflux, and unexplained dyspnea—remains central to reducing diagnostic delay and improving outcomes through earlier specialist referral and structured multiorgan screening.

Keywords: systemic sclerosis, scleroderma, Raynaud's phenomenon, puffy fingers, sclerodactyly, nailfold capillaroscopy, interstitial lung disease, pulmonary arterial hypertension, gastrointestinal dysmotility, scleroderma renal crisis, autoantibodies, clinical phenotype

Introduction

Systemic sclerosis, also termed systemic scleroderma, occupies a distinctive place among autoimmune rheumatic diseases because it combines vasculopathy, chronic immune activation, and progressive fibrosis within a single clinical framework, producing extraordinary variation in presentation, tempo, and outcome. Contemporary reviews define it as a rare orphan disease characterized by the triad of microvascular damage, autoimmune dysregulation, and fibrotic remodeling of the skin and internal organs, while recent epidemiological synthesis confirms that despite its low absolute prevalence, its morbidity and mortality remain disproportionately high relative to many more common rheumatologic disorders [1,2,5]. Current estimates suggest that the burden of systemic sclerosis is growing as recognition improves, with more recent analyses identifying global incidence in the range of approximately 1.4–8.6 per 100,000 person-years and prevalence near 17.6–18.9 per 100,000 individuals, although marked geographic, ethnic, and methodological variation persists [5]. Women are affected far more commonly than men, the disease most often arises in mid-adulthood, and several cohorts have shown earlier onset and more severe visceral disease in certain racial and ethnic populations, particularly in patients of African ancestry [2,5]. Clinically, systemic sclerosis is traditionally divided into limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis according to the extent of skin involvement, yet modern practice increasingly recognizes that this binary subdivision is only the first step in risk stratification, since organ complications may occur in every subset, including overlap disease and systemic sclerosis sine scleroderma [1-4]. The major problem in real-world care is not only complexity but delay: the 2024 British Society for Rheumatology guideline notes that diagnosis is often postponed because the earliest manifestations—Raynaud's phenomenon, reflux symptoms, arthralgia, edema of the hands, fatigue, and carpal tunnel syndrome—are nonspecific and are often encountered long before obvious skin thickening forces diagnostic clarity [4]. Indeed, average delays of more than a decade from the onset of Raynaud's phenomenon and more than a year from the onset of non-Raynaud symptoms have been described, which is clinically unacceptable in a disease where early diffuse forms may progress rapidly to irreversible lung, cardiac, or renal injury [4]. For this reason, the study of "distinctive clinical features" is not a descriptive luxury but a diagnostic imperative. The earliest vascular signals, such as persistent Raynaud's phenomenon with abnormal nailfold capillaroscopy, can precede fibrosis; the earliest inflammatory-fibrotic clues, such as puffy fingers, pruritic edematous hands, and evolving sclerodactyly, can distinguish incipient systemic sclerosis from benign primary Raynaud's phenomenon; and the earliest internal-organ complaints, such as heartburn, dysphagia, exertional dyspnea, or new hypertension, can point toward visceral involvement before advanced damage appears [2-8]. The 2013 ACR/EULAR classification criteria represented a major step forward because they captured this broader phenotype by incorporating not only proximal finger skin thickening but also fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and systemic sclerosis-specific autoantibodies [3]. Yet classification criteria do not replace clinical judgment, and the distinctive clinical profile of systemic sclerosis still demands careful bedside recognition supported by targeted laboratory, capillaroscopic, and imaging assessment [1-4]. In that context, the present article seeks to provide an IMRaD-structured narrative review of the characteristic clinical manifestations of systemic sclerosis, with emphasis on their diagnostic sequence, phenotype associations, organ-system clustering, and prognostic significance, in order to support earlier recognition and more rational surveillance in patients who may otherwise drift through the healthcare system until the disease has already declared its most dangerous forms.

Materials and Methods

This article was designed as a structured narrative review in IMRaD format because the topic concerns the synthesis of clinical manifestations rather than the presentation of new original cohort data. The evidence base was assembled from authoritative and recent sources that collectively cover classification, epidemiology, early diagnosis, phenotype evolution, organ-specific manifestations, and guideline-based clinical assessment in systemic sclerosis. Priority was given to high-quality reviews, guideline statements, and widely used classification frameworks, including the 2013 ACR/EULAR classification criteria, the 2024 British Society for Rheumatology guideline for management of systemic sclerosis, the 2025 epidemiological scoping review of systemic sclerosis and its organ manifestations, and recent focused reviews on interstitial lung disease, gastrointestinal disease, cardiac involvement, and autoantibody–phenotype correlations [3-5,9-13]. Foundational early-diagnosis literature was also included, particularly the Delphi-based preliminary criteria for very early systemic sclerosis, the VEDOSS multicentre analysis highlighting puffy fingers as a pivotal early sign, and the five-year longitudinal VEDOSS study examining progression from Raynaud's phenomenon to classifiable systemic sclerosis [6-8]. Organ-specific reviews were selected to ensure that the analysis of symptoms and signs remained clinically grounded rather than overly theoretical, while the NCBI/StatPearls overview was used as a concise synthesis of bedside manifestations and routine evaluation [2,9-12]. The review emphasized English-language literature, recent consensus, and clinically applicable evidence. Sources were included when they directly addressed one or more of the following domains: early vascular manifestations, cutaneous phenotype, musculoskeletal involvement, gastrointestinal dysfunction, pulmonary disease, cardiac disease, renal crisis, overlap syndromes, or serological phenotype stratification. The extracted material was interpreted with a clinical—not purely bibliometric—purpose: to identify which manifestations are most characteristic of systemic sclerosis, which combinations are most diagnostically informative, and which features carry specific prognostic implications. Because the article is a narrative synthesis rather than a meta-analysis, no formal pooled statistical model was applied; instead, recurring findings across guidelines, reviews, and landmark observational studies were integrated into a unified clinical framework. This approach is particularly appropriate for systemic sclerosis, where disease heterogeneity, variable definitions of organ involvement, and phenotype-specific trajectories make a purely numerical summary less informative than a clinician-oriented synthesis of patterns, warning signs, and organ-risk associations [2-13].

Results

The clinical phenotype of systemic sclerosis emerges as a layered continuum beginning with vascular dysfunction, expanding through cutaneous fibrosis, and eventually involving multiple organs with patterns that differ according to skin subset, autoantibody profile, and disease duration. In the earliest recognizable phase, Raynaud's phenomenon is usually the first symptom, but unlike benign primary Raynaud's phenomenon, secondary Raynaud's in systemic sclerosis is often more severe, may be associated with digital pain or ischemic change, and is accompanied by abnormal nailfold capillaries showing dilatation, hemorrhages, and capillary dropout [2,6-8]. This vascular beginning is not merely a prodrome; it is the first visible expression of the disease's core microangiopathy. The very early diagnosis literature has shown that puffy fingers are a particularly important red-flag sign, especially when they occur in a patient with Raynaud's phenomenon and systemic sclerosis-specific autoantibodies, because that combination carries high risk of progression to classifiable disease [6-8]. In the 2021 VEDOSS longitudinal study, absence of antinuclear antibodies strongly reduced progression risk, whereas increasing combinations of VEDOSS features progressively increased the likelihood that patients with Raynaud's phenomenon would fulfill systemic sclerosis classification criteria over time [8]. Once the disease enters its overt cutaneous phase, skin involvement

becomes the most visible hallmark. The 2013 ACR/EULAR classification system assigns sufficient weight to bilateral finger skin thickening extending proximal to the metacarpophalangeal joints to classify a patient immediately, but it also recognizes the importance of puffy fingers, sclerodactyly, fingertip pitting scars, digital ulcers, telangiectasia, and abnormal nailfold capillaries in patients without proximal skin thickening [3]. Clinically, the skin often evolves through an edematous puffy-hand period, followed by a fibrotic phase characterized by tight, thickened, leather-like skin, progressive loss of mobility, and eventual softening in selected areas after years of disease [2]. Sclerodactyly remains one of the most distinctive signs: the fingers become tapered, stiff, and flexed, and fine motor function deteriorates. Facial involvement adds a highly recognizable appearance marked by microstomia, perioral furrowing, reduced facial expressiveness, and a mask-like facies [2]. Pigmentary changes, particularly the classic salt-and-pepper pattern, further reinforce the diagnosis, while telangiectasias on the face, hands, lips, and mucosa indicate chronic microvascular injury and are clinically relevant because extensive telangiectasia correlates with pulmonary vascular risk [2,12]. Calcinosis, though more typical in limited cutaneous disease, contributes substantial morbidity through pain, recurrent inflammation, ulceration, drainage of chalky material, and secondary infection. Vascular damage in the hands extends beyond color change: digital pitting, ischemic ulcers, tissue loss, and, in severe cases, dry gangrene may occur, underscoring that systemic sclerosis is not merely a fibrotic skin disorder but a vasculopathic ischemic disease [2,4,12]. The distinction between limited and diffuse cutaneous forms remains clinically meaningful. Limited cutaneous disease usually affects the skin distal to the elbows and knees and the face, often with a longer antecedent history of Raynaud's phenomenon and a slower external course, whereas diffuse cutaneous disease extends proximally and to the trunk and is much more strongly associated with early internal-organ complications, especially in the first years after the first non-Raynaud manifestation [2,4,12]. However, modern guidelines emphasize that major organ disease can appear in any subset, so the old temptation to equate limited disease with mild disease is increasingly indefensible [4]. Musculoskeletal manifestations are also common and diagnostically helpful. Arthralgia, morning stiffness, tendon friction rubs, inflammatory arthritis-like patterns, myalgia, and reduced range of motion occur frequently and may be compounded by contractures imposed by skin tightening [2]. Tendon friction rubs are particularly important because they are more common in diffuse disease and are linked to poorer prognosis. Some patients develop inflammatory myopathy or fibrosing myopathy, leading to proximal weakness, functional decline, and worse outcomes. Carpal tunnel syndrome may appear early because edematous tissue compresses peripheral nerves [2]. Gastrointestinal involvement is among the most prevalent yet historically under-recognized domains of systemic sclerosis. Recent reviews argue that gastrointestinal disease remains the neglected organ system of systemic sclerosis despite its major effect on nutrition, quality of life, hospitalization, and even mortality [10]. Clinical expression can begin in the mouth and oropharynx, where reduced oral aperture impairs oral hygiene and eating, and sicca symptoms may reflect salivary fibrosis or secondary Sjögren overlap [2,10]. The esophagus is the most commonly involved segment; distal smooth-muscle dysfunction leads to dysphagia, chronic reflux, esophagitis, strictures, Barrett's esophagus, aspiration risk, and disturbed sleep [2,10]. In many patients, reflux is not a trivial complaint but an early clue to systemic disease. Gastric involvement can produce delayed emptying, bloating, nausea, early satiety, anorexia, and weight loss. Gastric antral vascular ectasia, often called watermelon stomach, may cause chronic occult blood loss or overt bleeding [2]. Small bowel disease contributes bloating, abdominal pain, bacterial overgrowth, malabsorption, nutritional depletion, vitamin deficiencies, and pseudo-obstruction, while anorectal involvement leads to urgency, passive leakage, and fecal

incontinence that is often underreported because it is socially embarrassing yet clinically devastating [2,10]. Pulmonary disease remains the principal determinant of mortality in many cohorts. Interstitial lung disease affects a large proportion of patients with systemic sclerosis, with modern reviews citing involvement in approximately 65% of patients and roughly 40% of systemic sclerosis-related deaths attributable to this domain [9]. Clinically significant interstitial lung disease may initially be silent, which is why reliance on symptoms alone is dangerous. When symptoms develop, exertional dyspnea, fatigue, and dry cough predominate; bibasilar crackles, reduced diffusion capacity, restrictive physiology, and high-resolution CT evidence of nonspecific interstitial pneumonia are common [2,4,9,12]. Diffuse cutaneous disease and anti-topoisomerase I positivity are particularly associated with early and sometimes rapidly progressive fibrotic lung disease [2,12]. Pulmonary arterial hypertension represents another major and often later cardiopulmonary manifestation, especially in vascular-dominant phenotypes and certain limited cutaneous subsets; clinically it presents with progressive exertional dyspnea, fatigue, chest discomfort, edema, presyncope, or syncope, often after an initially subtle phase marked only by reduced DLCO or elevated biomarkers [2,4,13]. Because pulmonary vascular disease may remain occult until advanced, the 2024 BSR guideline recommends annual screening using pulmonary function tests, echocardiography, NT-proBNP, and the DETECT strategy in appropriate patients [4]. Cardiac involvement is increasingly recognized as both frequent and underdiagnosed. Recent reviews describe primary heart involvement as a spectrum that includes arrhythmias, conduction abnormalities, myocarditis-like inflammation, myocardial fibrosis, diastolic and systolic dysfunction, pericardial disease, and heart failure, often with a subclinical course that can masquerade as other cardiomyopathies [11]. Clinically, patients may report palpitations, exercise intolerance, atypical chest discomfort, presyncope, or simply disproportionate fatigue. Objective clues may include elevated troponin or natriuretic peptides, ECG abnormalities, echocardiographic dysfunction, or cardiac MRI evidence of fibrosis and inflammation [4,11]. Pericardial effusions are often small but clinically meaningful; in some cohorts, they are associated with diffuse disease and with scleroderma renal crisis risk [2,11]. Renal involvement is dominated by scleroderma renal crisis, a dramatic syndrome of new-onset hypertension or malignant hypertension, acute kidney injury, microangiopathic hemolytic anemia, thrombocytopenia, and rapidly progressive renal failure, classically arising in early diffuse disease and strongly associated with anti-RNA polymerase III antibodies and corticosteroid exposure [2,12,13]. Although less common than lung or gastrointestinal involvement, renal crisis retains enormous clinical importance because recognition must be immediate. Another distinctive element of the systemic sclerosis phenotype is serological clustering. Autoantibodies are not merely diagnostic ornaments; they correspond to recognizable clinical patterns [4,12]. Anticentromere antibodies are most often associated with limited cutaneous disease, long-standing Raynaud's phenomenon, telangiectasia, calcinosis, digital ischemic complications, relatively lower risk of fibrotic ILD, and higher long-term risk of pulmonary arterial hypertension [12]. Anti-topoisomerase I antibodies are enriched in diffuse cutaneous disease and strongly linked to interstitial lung disease, earlier fibrotic progression, and digital ulcers [2,12]. Anti-RNA polymerase III antibodies are associated with rapidly progressive skin disease, edematous hands, tendon friction rubs, and markedly elevated renal crisis risk, with important literature also suggesting a close temporal relationship between disease onset and malignancy in some patients [4,12]. Less common antibodies such as U3-RNP/fibrillarin, Th/To, PM-Scl, Ku, and U1-RNP help identify overlap or special phenotypes that may emphasize pulmonary hypertension, gastrointestinal dysmotility, myositis, arthritis, or mixed connective-tissue features [12]. Finally, several atypical presentations broaden the disease's clinical boundaries. Overlap syndromes with myositis, rheumatoid arthritis,

or Sjögren syndrome are not rare and may obscure diagnosis. Systemic sclerosis sine scleroderma is especially important because patients may present with Raynaud's phenomenon, abnormal capillaroscopy, positive autoantibodies, pulmonary or gastrointestinal involvement, and no obvious skin thickening, proving that the absence of hard skin does not exclude systemic sclerosis [2,4]. Taken together, these findings show that the most distinctive clinical signature of systemic sclerosis is not a single sign but a reproducible constellation: severe or persistent Raynaud's phenomenon, puffy fingers, capillaroscopic microangiopathy, evolving skin thickening, digital lesions, telangiectasia, reflux or dysphagia, exertional dyspnea, serology-based phenotype clues, and the ever-present possibility of silent visceral progression beneath an apparently limited external phenotype [2-13].

Discussion

The synthesis of current evidence indicates that the clinical distinctiveness of systemic sclerosis lies in the patterned coexistence of vascular, fibrotic, inflammatory, and organ-specific manifestations rather than in any one isolated symptom. This has several major implications. First, diagnosis must become phenotype-oriented rather than event-oriented. Waiting for advanced skin thickening before suspecting systemic sclerosis is inconsistent with contemporary knowledge, because the disease often announces itself through persistent Raynaud's phenomenon, puffy fingers, telangiectasia, reflux, or abnormal capillaroscopy long before a classic textbook picture is complete [4,6-8]. Second, the old clinical habit of treating external extent of skin disease as the sole determinant of severity should be abandoned. Skin subset remains useful, but the 2024 BSR guideline correctly emphasizes that organ-based complications may develop in all subsets, including overlap and sine scleroderma phenotypes, and that risk stratification should combine skin subtype with antibody subset and systematic screening [4]. Third, the organ systems most responsible for disability are not always the most visible. Gastrointestinal disease can be more burdensome to daily life than skin fibrosis yet is still frequently under-recognized; cardiac disease may remain subclinical until substantial myocardial injury has occurred; interstitial lung disease may progress despite minimal respiratory symptoms; and pulmonary arterial hypertension may hide behind unexplained fatigue or a declining DLCO until right-heart dysfunction is established [4,9-11]. This means that distinctive clinical features should be understood in two layers: the visible layer that raises suspicion and the latent layer that must be actively screened for once suspicion exists. Fourth, the significance of autoantibodies should be interpreted clinically, not mechanically. Their greatest value is not that they make the diagnosis in isolation, but that they organize expectation: anticentromere suggests vascular-limited disease with later pulmonary vascular risk; anti-topoisomerase I suggests lung-dominant fibrotic risk; anti-RNA polymerase III suggests explosive skin progression and renal crisis vulnerability; and overlap-associated antibodies suggest muscle, joint, or mixed connective tissue phenotypes [4,12]. Such serological pattern recognition converts laboratory data into a practical surveillance plan. Fifth, the VEDOSS literature changes the philosophy of case finding. Patients with Raynaud's phenomenon plus puffy fingers, specific autoantibodies, or capillaroscopic abnormalities do not merely have possible autoimmune disease; they occupy a biologically meaningful at-risk stage in which structured follow-up is justified [6-8]. This is where early clinical literacy matters most. A clinician who notices puffy fingers and asks about reflux, dyspnea, and digital ulcers may alter prognosis more effectively than one who orders a broad antibody panel without a phenotypic framework. Sixth, the burden of systemic sclerosis is best conceptualized as cumulative and interactional. Esophageal dysfunction promotes aspiration and worsens lung disease; malnutrition worsens muscle weakness and frailty; pulmonary hypertension and myocardial fibrosis amplify exercise limitation; renal crisis may complicate an already unstable multisystem state. The disease behaves less like isolated organ involvement and more like a network disorder in which vascular injury and

fibrosis unfold across connected physiological systems [1,4,9-13]. Finally, current guideline evolution reinforces that accurate clinical phenotyping is not just diagnostic but therapeutic. The updated EULAR recommendations explicitly organize treatment across organ domains, reflecting the reality that systemic sclerosis care now depends on early recognition of which clinical domain is active or threatened—Raynaud's phenomenon, digital ulcers, skin fibrosis, ILD, PAH, SRC, gastrointestinal disease, or inflammatory musculoskeletal overlap [13]. Therefore, the most useful conclusion from this review is practical: the clinician should suspect systemic sclerosis early, classify it broadly, stratify it biologically, screen it systematically, and never let a limited external phenotype create false reassurance. In systemic sclerosis, the quiet patient with puffy fingers and heartburn may be far more urgent than the dramatic rash in another disease; the illness is a master of understatements until it is not.

Conclusion

Systemic sclerosis should be approached clinically as a dynamic multisystem phenotype whose earliest clues are often vascular and deceptively modest, whose most visible manifestations are cutaneous, and whose most consequential outcomes are determined by silent or progressive internal-organ involvement. The review demonstrates that the distinctive clinical profile of systemic sclerosis is anchored in a recognizable sequence of manifestations: persistent or severe Raynaud's phenomenon, puffy fingers, abnormal nailfold capillaroscopy, evolving sclerodactyly, digital ischemic lesions, telangiectasia, gastrointestinal dysmotility, interstitial lung disease, pulmonary vascular disease, cardiac abnormalities, and, in selected high-risk phenotypes, scleroderma renal crisis. The combination and timing of these manifestations matter as much as their presence. Limited cutaneous and diffuse cutaneous forms remain useful clinical categories, but prognosis is more accurately shaped by organ pattern and autoantibody context than by skin extent alone. Very early diagnosis frameworks and contemporary guidelines now make it clear that early suspicion, early referral, and structured longitudinal screening are central to improving outcomes. In practical terms, the clinician who recognizes the phenotype early can transform a delayed diagnosis into a monitored disease trajectory in which lung function, pulmonary pressure, gastrointestinal status, cardiac integrity, blood pressure, and renal function are actively protected rather than passively observed. Thus, the true distinctive feature of systemic sclerosis is not simply skin hardening, but the convergence of microangiopathy, fibrosis, and organ-selective dysfunction in a disease that requires an alert eye, disciplined surveillance, and phenotype-guided management from its earliest stages.

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