Original paper

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Prevalence and severity of complicated Raynaud's phenomenon in limited and diffuse systemic sclerosis: a multicenter study in Iraq

Farah Jaafar[1], Zakariya Moayad[2], Faiq Gorial[3], Ali Alkazzaz[2]

[1]Rheumatology Unit, Department of Medicine, College of Medicine, University of Mustansiriyah, Iraq
[2]Rheumatology Unit, Department of Medicine, College of Medicine, University of Babylon, Iraq
[3]Rheumatology Unit, Department of Medicine, College of Medicine, University of Baghdad, Iraq

Abstract

Introduction: Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease with multiple internal organ involvement, vasculopathy, and fibrosis. Two major types are present, limited systemic sclerosis (lSSc) and diffuse systemic sclerosis (dSSc), according to the limit of skin fibrosis, with variability in internal organ involvement. Raynaud's phenomenon (RP) is almost always present in either type as a presenting feature; it may precede the onset by years. It affects the quality of life for the patient and has a variable range of complications as well, with the most severe being tissue gangrene and finger amputation. The aim of the study was to investigate the prevalence of RP complications and predictors of outcome in lSSc and dSSc.

Material and methods: Patients diagnosed with SSc were included in the study at 3 rheumatology centers in Iraq over a 3-year period. Data collection was conducted through questionnaires and interviews. All patients underwent clinical assessments to determine the presence or absence of RP complications, including pit scars, ulcers, ischemia, and amputated digits at the time of interview as well as the previous records. Subjects with concomitant autoimmune diseases were excluded from the study.

Results: Of the 105 patients, 55 (52%) had dSSc, and 92% of those were female. The mean age was in the fourth decade. Digital complications were recorded. Ischemia was the most frequently observed complication in limited scleroderma, while amputation was the least common. These complications exhibited a significant association with the duration of the disease, with the highest prevalence occurring within the first 10 years of diagnosis. Cardiac complications were associated with RP. Notably, 27% of patients with dSSc had hypertension, while 64% of patients with limited scleroderma did not have cardiac complications.

Conclusions: Raynaud's phenomenon is a defining characteristic of both limited and diffuse scleroderma. It is particularly complex in the diffuse form, underscoring the necessity for aggressive treatment to prevent debilitating complications. It is crucial to educate patients about the significance of adhering to treatment regimens and cessation of smoking.

Key words: Raynaud's phenomenon, scleroderma, ischemia.

Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease with a complex pathogenesis, diverse clinical manifestations, and variable natural history. Autoimmunity, functional and structural alterations in small blood vessels, and widespread interstitial and vascular fibrosis affecting the skin are the hallmarks of this disease. Prevalence is 10–20 per 100,000; it affects women more commonly than men (4 : 1), with the peak age of onset being in the fourth and fifth decades.

Scleroderma is classified into 2 major types: generalized and localized (which includes morphea and linear scleroderma). Generalized sclerosis is subclassified

Address for correspondence
Farah Jaafar, Rheumatology Unit, Department of Medicine, College of Medicine, University of Mustansiriyah, Alkarkh St., postcode: 10021, Iraq, e-mail: dr.farah_jaafar@uomustansiriyah.edu.iq
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according to the level of skin involvement into limited systemic sclerosis (lSSc; which is more common in two-thirds of cases) and diffuse systemic sclerosis (dSSc) [1].

Systemic sclerosis is associated with systemic manifestations and internal organ involvement, which is not the case in localized scleroderma, as it is limited to the skin and subcutaneous tissues only. The clinical manifestation of this disease reflects the underlying pathogenic triad of microangiopathy, immune dysregulation, and subsequent systemic fibrosis. It affects the skin, lung, heart, gastrointestinal, and other internal organs.

Almost all SSc patients suffer from Raynaud's phenomenon (RP), which is defined as triphasic intermittent, excessive vasoconstriction of the microvasculature. Typically, it is the initial manifestation of the disease and may precede the involvement of other organs by many years, especially in lSSc, which might cause impaired hand function, pain, and reduced quality of life, particularly in cold weather [2]. This needs urgent intervention to restore the vascular supply, as if it is left untreated, it may lead to ischemia, ulceration, or gangrene, which might lead to autoamputation [3].

In scleroderma microangiopathy, a combination of intimal proliferation, hypertrophied media, and fibrosing adventitia along with defective revascularization results in progressive narrowing of the vascular lumen and ischemia [4]. This study aimed to determine which one of the SSc types (limited vs. diffuse) is associated more frequently with these complications.

Material and methods

This was a retrospective, descriptive study. All patients with SSc and RP were included in the study during their visits to the Rheumatology Consultant Clinic at 3 rheumatology centers in Iraq (Al-Yarmouk Teaching Hospital, Baghdad Hospital/Medical City Complex, and AL-Marjan Hospital) in Baghdad and Babylon between 2020 and 2023. Data collection involved questionnaires and interviews after obtaining informed consent from each patient. Socio-demographic characteristics, disease duration, and clinical data were recorded for all patients. At the time of interview, all patients underwent clinical assessments to determine the presence or absence of RP complications, including pit scars, ulcers, ischemia, and amputated digits. They were also asked about any previous occurrences of these complications, and their medical records were reviewed for additional information.

Inclusion and exclusion criteria

Inclusion criteria:

- adult patients with SSc and RP, meeting the 2013 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for SSc [5].

Exclusion criteria:

- refusal to participate in the study,
- subjects with SSc overlapping with other autoimmune diseases that could generate confounding biases (rheumatoid arthritis, vasculitis, lupus, antiphospholipid syndrome),
- individuals with hematological disorders and associated prothrombotic disease,
- patients with associated thromboembolic diseases.

Statistical analysis

Analysis of data was carried out using SPSS version 26 (IBM Corp., Armonk, NY, USA). Results were presented as frequency, percentage, mean, standard deviation, and range (maximum–minimum).

Differences in percentages (qualitative data) were tested using the Pearson χ^2 test with application of Yate's correction or Fisher's exact test whenever applicable. Statistical significance was set at $p < 0.05$.

Bioethical standards

The study protocol was approved after review and official permission was obtained from the Ethics Committee in the Medical Department, College of Medicine, University of Baghdad (approval No. 125).

Results

A total of 105 patients were included in the study. Fifty-five of them had dSSc. Ninety-two percent were female (Table I), reflecting the higher frequency of the disease in females. The *p*-value of gender association was 0.02, which indicates a significant association. The mean age of the disease was in the fourth decade. There was a significant association with educational level ($p = 0.001$). In dSSc, it was most common in those with primary school education (61%), while in lSSc it had similar prevalence in primary and secondary school graduates (28%). In both types of scleroderma, most patients had a normal body mass index (Table II).

Digital complications were recorded (Table II); most of those with RP were uncomplicated. Ischemia was most commonly noted in lSSc, while the most severe complication (amputation) was the least common one in the study population and was seen only in dSSc, which is known to be associated with poor vascular outcomes and difficult to treat. These complications were significantly associated with the duration of the disease, being more commonly observed within 10 years after the diagnosis than in later years (Table III).

Table I. Sociodemographic characteristics of study population

Variables	dSSc (*n* = 55)	lSSc (*n* = 50)	*p*
Age [years], mean ±SD	42.78 ±17.14	43.36 ±14.57	0.85
Sex [*n* (%)]			
Male	4 (7.27)	3 (6)	0.02
Female	51 (92.7)	47 (94)	
Body mass index [kg/m^2], mean ±SD	23.5 ±2.24	22.7 ±1.71	0.54
Educational level [*n* (%)]			
Illiterate	10 (18.18)	11 (22)	0.001
Primary	34 (61.81)	14 (28)	
Secondary	9 (16.3)	14 (28)	
College	2 (3.6)	11 (22)	
Smoking [*n* (%)]			
Non-smoker	33 (60)	31 (62)	0.16
Passive smoker	20 (36.36)	12 (24)	
Ex-smoker	2 (3.63)	5 (10)	
Smoker	0 (0)	2 (4)	

dSSc – diffuse systemic sclerosis, lSSc – limited systemic sclerosis.

Table II. Statistical association of digital complications in diffuse and limited scleroderma

Digital complications	dSSc (*n* = 55)	lSSc (*n* = 50)	Total (*n* = 105)	*p*
Amputation [*n* (%)]	3 (5.45)	0 (0)	3 (2.85)	0.424
Ischemia [*n* (%)]	7 (12.72)	12 (24)	19 (18.09)	
Pit scars [*n* (%)]	15 (27.27)	11 (22)	26 (24.76)	
Ulcer [*n* (%)]	12 (21.81)	11 (22)	23 (21.90)	
Uncomplicated [*n* (%)]	18 (32.72)	16 (32)	34 (32.38)	

dSSc – diffuse systemic sclerosis, lSSc – limited systemic sclerosis.

Table III. Statistical association of digital complications in relation to duration of disease

Duration of disease [years]	Amputation [*n* (%)]	Ischemia [*n* (%)]	Pit scars [*n* (%)]	Ulcer [*n* (%)]	Uncomplicated [*n* (%)]	*p*
1–10	1 (33.33)	10 (52.63)	21 (80.7)	19 (82.60)	29 (85.29)	0.0001
11–20	1 (33.33)	9 (47.36)	5 (19.23)	3 (13.04)	4 (11.76)	
21–30	1 (33.33)	0 (0)	0 (0)	1 (4.34)	1 (2.94)	
Total	3	19	26	23	34	

The association between the type of treatment and RP complications was also investigated. Notably, out of the 105 patients included in the study, 11 patients were using low-dose glucocorticosteroids (GCs) as part of their treatment at the time of the study. Two of these patients were using GCs due to active arthritis, while the remaining 9 were using them due to interstitial lung disease (ILD), as they had previously been treated by non-rheumatologist general physicians for various reasons. Amputation was most commonly noted in those using 3 lines including GCs and disease-modifying antirheumatic drugs (DMARDs), while none was present for those on calcium channel blockers or antiplatelet agents in combination with DMARDs (Table IV). This finding is consistent with the protective vasodilator effect of calcium channel blockers, which are the first-line therapy in RP patients.

Echocardiographic findings were assessed (Table V); 70% of lSSc patients had no cardiac complications at all. Pulmonary arterial hypertension (PAH) on echocardiography was the most common finding in dSSc (52% of cases), in contrast to the results of other studies sug-

Table IV. Association of digital complications in relation to type of treatment in diffuse vs. limited scleroderma

Type of treatment	Amputation [*n* (%)]	Ischemia [*n* (%)]	Pit scars [*n* (%)]	Ulcer [*n* (%)]	Uncomplicated [*n* (%)]	*p*
DMARD + CCB	0 (0)	3 (15.78)	5 (19.20)	10 (43.70)	9 (26.47)	0.001
DMARD + antiplatelet	0 (0)	0 (0)	0 (0)	0 (0)	5 (14.70)	
DMARD + CCB + GC	2 (66.66)	3 (15.78)	3 (11.53)	3 (13.04)	7(20.58)	
Total	3	19	26	23	34	

CCB – calcium channel blocker, DMARD – disease-modifying antirheumatic drug, GC – glucocorticosteroid.

Table V. Association of cardiac complication with diffuse and limited systemic sclerosis

Echocardiographic findings [n (%)]	dSSc (*n* = 55)	lSSc (*n* = 50)	*p*
Normal	20 (36.36)	35 (70)	0.001
Pulmonary hypertension	29 (52.72)	8 (16)	
Ischemic heart disease	4 (7.27)	5 (10)	
Valvular heart disease	2 (3.63)	2 (4)	

dSSc – diffuse systemic sclerosis, lSSc – limited systemic sclerosis.

Table VI. Association of cigarette smoking status and RP complications

Smoking status	Complication status	No. of patients	*p*
Non-smoker	Complicated	37	0.163
	Uncomplicated	28	
Smoker	Complicated	29	
	Uncomplicated	11	

gesting that it is more common in limited rather than diffuse scleroderma patients. Complicated RP was noted most commonly in nonsmokers, while 29 of those who had ever been exposed to smoke had complicated RP (Table VI). This finding may be explained by the predominance of nonsmokers in the study population.

Discussion

Systemic sclerosis is a rare autoimmune disease with multisystemic involvement, vasculopathy, and fibrosis [6, 7]. Its hallmark feature is skin thickening, the extent of which depends on the subtype of scleroderma, with the elbows and knees serving as anatomical landmarks. One of the most common manifestations is RP, which is almost always present and may precede other clinical features by more than 10 years.

Raynaud's phenomenon is a triphasic vascular condition in which accelerated cold-induced vasoconstriction of the digital arteries causes pallor followed by cyanosis and finally reactive hyperemia. It is associated with endothelial dysfunction of the microvasculature and an abnormal immune response [8]. Pain and paresthesia are the main symptoms of RP in SSc. Nailfold capillaroscopy, a commonly used bedside tool, is typically used to evaluate whether RP is primary or secondary to underlying connective tissue disease. It is particularly useful in distinguishing patients with primary RP from those with scleroderma or other rheumatic diseases. Moreover, the utility of assessing patterns of nailfold capillary abnormalities has been reported in monitoring the progression of the disease toward more severe manifestations.

The patterns of capillary abnormalities appear to correlate with the progression of systemic disease manifestations in SSc. In the early pattern of SSc microangiopathy, there is no disorganization of the capillaries. Later on, dilated capillaries, microhemorrhages, and disorganized capillary networks are characteristic of SSc, while dropouts, avascular areas, and signs of neovascularization with distorted architecture manifest at later stages of the disease [9]. The duration of RP in the pre-diagnostic stage of SSc tends to be longer in lSSc. Moinzadeh et al.'s study [10] revealed that in patients with RP who exhibited negative serology and normal nailfold capillaroscopy on subsequent follow-up visits, there was no progression to connective tissue disease over time [10].

In the case of a persistent vasoconstriction, significant tissue ischemia may develop, resulting in digital ulcers. This tendency to have digital ulcers in SSc can be explained by repeated microtrauma of the thinned, dry skin and calcinosis. From 8% to 12% of those with digital ulcers have underlying calcinosis [11]. It was estimated that 40–50% of all SSc patients experience digital ulcers; recurrent digital ulcers develop in 31–71% of those patients, and 30% of those with persistent digital ulcers will have permanent tissue loss [12].

Risk factors for developing digital ulcers are male sex, a diffuse subset of the disease, early onset of SSc, presence of pulmonary hypertension, presence of anti-topoisomerase I antibodies, and cigarette smoking. Digital ulcers are associated with the development of internal organ involvement 2–3 years earlier compared to those without ulcers [13].

Hughes et al. [14] stated in his article that approximately 75% of scleroderma patients will go on to develop their first digital ulcer within 5 years of the diagnosis. Similarly, this study found that 85% of those with digital ulcers were in the first 10 years of the disease.

Episodes of RP can be provoked by cold exposure, emotional stress, and ambient temperature changes. It can be prevented by avoiding cold exposure, maintaining the core body temperature, and wearing gloves [15].

Treatment of RP basically depends on vasodilators. First-line treatment is calcium channel blockers, then add-on therapies can be used in non-respondents; the effectiveness of vasoactive treatment is rated modestly, with only 21% of secondary RP respondents considering their RP treatment effective. Smoking does not appear to influence vasoactive therapy use for SSc-RP [16, 17]. In severe cases, and in those with failure of first-line therapy, intravenous iloprost can be used, as it reduces the frequency and severity of RP attacks [18]. A high dose of vitamin C > 1,000 mg per day should be avoided, as it stimulates collagen formation and enhances its deposition [19].

Although endothelin receptor blockers with bosentan are used mainly to prevent development of new digital ulcers in scleroderma patients, it does not affect the healing period of the ulcers that are already present [20].

Smoking is an important factor that has been widely studied to evaluate its association with RP outcome. Current smokers were 3–4 times more likely than those who never smoked to develop digital vascular complications. In this study, there was no statistically significant correlation between smoking status and the presence of complications; similarly, Cherumi et al. [21] found that past smokers were not at increased risk in comparison with nonsmokers.

Suter et al. [22] included 1,840 women and 1,602 men in their study; they concluded that current smoking was associated with RP in men, but not in women. This difference can be explained by the larger sample size used in the study.

Pulmonary arterial hypertension is characterized by an elevated mean pulmonary artery arterial pressure exceeding 20 mmHg, a pulmonary vascular resistance of ≥ 3 Wood units, and a pulmonary artery wedge pressure of ≤ 15 mmHg, as determined by right heart catheterization, in the absence of substantial ILD [23].

Pulmonary arterial hypertension is the leading cause of death in SSc. It affects approximately 12% of all patients with SSc and carries a mortality rate of 50% within the first 3 years of its diagnosis [24]. In SSc, PAH can manifest in various forms. In cases where SSc is associated with ILD, PAH can be classified as group 3, primarily due to chronic lung disease and/or hypoxia. Individuals with myocardial fibrosis in SSc develop group 2 PAH. Additionally, primary biliary cirrhosis is a common occurrence in SSc and can lead to the development of porto-pulmonary PAH [25]. It was thought that PAH predominantly affects those with lSSc. Nevertheless, our study and some others have shown that it may also occur in patients with dSSc [26]. This might be explained by the higher prevalence of ILD in this group.

Strengths and limitations of the study

Strengths of this article include its multicenter data collection, which contributes to the number of patients diagnosed with this rare disease and highlights the diversity of its manifestations. Additionally, it aims to establish predictors for RP complications.

A limitation of this study is the absence of a more extended follow-up period conducted prospectively to evaluate the potential future complications of RP. Given its rarity, socioeconomic barriers, and the challenges associated with regular visits in rural and remote areas, it is difficult to conduct comprehensive assessments. Although nailfold capillaroscopy is an important tool in SSc research, it was not used in this study due to its limited availability in the outpatient clinic of Iraqi hospitals, which are constrained by financial limitations.

Conclusions

Raynaud's phenomenon is a defining feature of both limited and diffuse types of scleroderma. It tends to be more complicated in the diffuse type. Severe RP with its associated complications occurs especially in dSSc in the first years following disease onset.

These findings highlight the need for aggressive treatment to prevent such disabling complications. It is important to educate patients about the importance of compliance with treatment and quitting smoking.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

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Ethics approval: The study was approved by the Ethics Committee of the Medical Department, College of Medicine, University of Baghdad, Iraq (approval No. 125).

Data availability: The data that support the findings of this study are available on request from the corresponding author (F.J.).

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