



HAL
open science

Association of skin hyperpigmentation disorders with digital ulcers in systemic sclerosis: Analysis of a cohort of 239 patients

Vaianu Leroy, Pauline Henrot, Thomas Barnetche, Muriel Cario, Anne-Sophie Darrigade, Pauline Manicki, Marie-Sylvie Doutre, Estibaliz Lazaro, Joel Constans, Damien Barcat, et al.

► To cite this version:

Vaianu Leroy, Pauline Henrot, Thomas Barnetche, Muriel Cario, Anne-Sophie Darrigade, et al.. Association of skin hyperpigmentation disorders with digital ulcers in systemic sclerosis: Analysis of a cohort of 239 patients. *Journal of The American Academy of Dermatology*, 2019, 80, pp.478 - 484. 10.1016/j.jaad.2018.07.033 . hal-03484656

HAL Id: hal-03484656

<https://hal.science/hal-03484656>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

<LRH> *Vaianu et al*

<DOC>Original Article

<AT> **Association of skin hyperpigmentation disorders with digital ulcers in systemic sclerosis: Analysis of a cohort of 239 patients**

<AU> Vaianu Leroy, MD,^a Pauline Henrot, MD,^{b,c} MD, Thomas Barnetche, PhD,^b Muriel Cario-André, PhD,^c Anne-Sophie Darrigade, MD,^a Pauline Manicki, MD,^b Marie-Sylvie Doutre, MS,^a Estibaliz Lazaro, MD, PhD,^d Joel Constans, MD, PhD,^e Damien Barcat, MD,^f Vernhes Jean-Philippe, MD,^g Richez Christophe, MD, PhD,^b Taieb Alain, MD, PhD,^{a,c} Marie-Elise Truchetet, MD, PhD,^{b,f} and Julien Seneschal, MD, PhD,^{a,c} on behalf of the FHU ACRONIM.

<CITY> *Bordeaux, France*

<AFN> From the Department of Dermatology, National Reference Center for Rare Skin Disorders,^a and Department of Vascular Medicine, Hôpital Saint-André,^c Department of Rheumatology, Hôpital Pellegrin,^b and Department of Internal Medicine, Hôpital Haut-Levêque, CHU de Bordeaux^d; Inserm U1035, BMGIC, University of Bordeaux^c; and Department of Internal Medicine^f and Department of Rheumatology, Hôpital Robert Boulin, Libourne.^g

<ARTFN> Dr Leroy and Dr Henrot contributed equally to this study, and Dr Truchetet and Dr Seneschal contributed equally to this study.

<ARTFN> Funding sources: None.

<ARTFN> Conflicts of interest: None disclosed.

<ARTFN> Accepted for publication July 26, 2018.

<COR>Correspondence to: Julien Seneschal, MD, PhD, Department of Dermatology, Hôpital Saint-André, CHU de Bordeaux, 1 rue Jean Berguet, Bordeaux 33075, France. E-mail: julien.seneschal@chu-bordeaux.fr

<BEGIN ABSTRACT>

Background: Skin pigmentation disorders in systemic sclerosis (SSc) have been sparsely described in the literature. Nevertheless, they could be a diagnostic and/or severity marker.

Objectives: To assess the association between pigmentation disorders and systemic involvement in patients with SSc.

Methods: A total of 5 patterns of skin pigmentation disorders were defined: diffuse hyperpigmentation; hyperpigmentation of sun-exposed areas; hypopigmentation of the head, neck, and/or upper part of the chest; acral hypopigmentation; and diffuse hypopigmentation.

Results: A total of 239 patients were included; 88 patients (36.8%) had skin pigmentation disorders as follows: diffuse hyperpigmentation and hyperpigmentation of sun-exposed areas in 38.6% (n = 34) and 27.3% (n = 24) of patients, respectively; hypopigmentation of the face, neck, and/or chest in 10.2% of patients (n = 9); diffuse hypopigmentation in 12.5% (n = 11); and acral hypopigmentation in 17% (n = 15). Diffuse hyperpigmentation was associated with diffuse SSc ($P = .001$), increased modified Rodnan skin score ($P = .001$), and shorter duration of Raynaud phenomenon ($P = .002$) in univariate analysis but not in multivariate analysis. Moreover, diffuse hyperpigmentation was associated with digital ulcers ($P = .005$), as confirmed by multivariate analysis (odds ratio, 2.96; 95% confidence interval, 1.28-6.89).

Limitations: This was a single-center retrospective study of a cohort of patients with SSc.

Conclusion: Screening for skin pigmentation disorders could be useful in the management of patients with SSc to identify those with a high risk of development of digital ulcers, which is a symptom of vascular involvement in SSc.

<KW>**Key words:** digital ulcers; pigmentation; systemic sclerosis.

<END ABSTRACT>

CAPSULE SUMMARY

- Skin pigmentation abnormalities are classically associated with systemic sclerosis.
- Diffuse hyperpigmentation is associated with digital ulcers in systemic sclerosis.
- Screening for skin pigmentation disorders could be useful to identify patients with a high risk of development of digital ulcers, which are a clinical symptom of vascular involvement in systemic sclerosis.

<BEGIN ARTICLE>

Systemic sclerosis (SSc) is a rare and severe autoimmune disease leading to organ involvement and high rates of mortality and morbidity.^{1,2} Despite recent progress in the management of the disease, its course remains unpredictable. Recently, the validation of new classification criteria allowed for earlier detection of the disease, leading to better management before the development of irreversible complications. However, the identification of patients at risk of developing severe organ damage as digital ulcers and/or vascular involvement remains a challenge.

Skin pigmentation disorders associated with SSc have long been described in the literature and were first mentioned in 1898.³ The prevalence of pigmentation disorders associated with SSc has been reported to vary from 30.5%⁴ to 91%,⁵ with higher prevalence in Hispanics and African Americans than in whites, suggesting that this phenotype may be associated with darker phototypes.⁶ Several patterns of skin pigmentation disorders have been

described so far.⁷⁻¹⁶ The 3 most frequently described types are vitiligo-like depigmentation with perifollicular hyperpigmentation (also called salt-and-pepper skin),^{7,12,15} diffuse hyperpigmentation with accentuation in sun-exposed areas,^{4,5,16} and combined hyperpigmentation and hypopigmentation localized in the areas of sclerosis.

However, studies analyzing skin pigmentation disorders associated with SSc remain mostly descriptive. Therefore, we sought to better define the prevalence and patterns of skin pigmentation observed in SSc and to investigate the association between skin pigmentation disorders and the clinical or biologic characteristics of patients with SSc.

<H1>PATIENTS AND METHODS

<H2>Patients

This single-center retrospective study was conducted from January 2012 to March 2017. Patients with SSc were included in the Vasculopathy and Inflammation in Systemic Sclerosis research project (institutional ethics committee CPP, 2012-A00081-42, Aquitaine). All patients satisfied the American College of Rheumatology/European League against Rheumatism 2013 classification criteria for SSc¹⁷ and provided written informed consent. For each patient, a disease questionnaire was completed by the clinician. Clinical features (SSc type; sex; age at onset of Raynaud phenomenon [RP]; disease duration defined as the time since the occurrence of the first symptom other than RP; symptoms of skin and skin pigmentation disorders; and articular, heart, lung, kidney, and/or gastrointestinal involvement), results of immunologic tests (for antinuclear antibodies, antitopoisomerase antibodies, anticentromere antibodies, and anti-RNA polymerase III antibodies), and results of imaging and functional examination (thorax computed tomography scans, respiratory function tests, cardiac ultrasonography, and right-sided heart catheterization) were recorded. When several values for the same variable were recorded in the medical file, the worst value was registered for each patient. In the event of the presence of skin pigmentation abnormalities,

patients were systematically contacted by a dermatologist for clinical examination. The data recorded included skin phototype, skin tanning capacity, type (hyperpigmentation or hypopigmentation) and localization of the pigmentation disorders, and date of onset. When patients were not available, the physician in charge of the patients was contacted.

<H2>Patterns of pigmentation disorders

We defined 5 patterns of skin pigmentation disorders in patients with SSc according to the localization and type of pigmentation abnormalities (hyperpigmentation or hypopigmentation) as shown in Figs 1 and 2: (1) a diffuse skin hyperpigmentation pattern affecting the entire skin; (2) skin hyperpigmentation localized on sun-exposed areas; (3) skin hypopigmentation localized on the face (forehead), neck, upper part of the chest, and/or upper part of the back; (4) diffuse hypopigmentation affecting the limbs and trunk; and (5) skin hypopigmentation with hypopigmented macules distributed mainly on acral areas (forearms, hands, lower part of the legs, and feet).

When patients presented with more than 1 pattern, they were classified as having the most suitable pattern. Five patients who had both significant hypopigmentation and hyperpigmentation were classified as having 2 patterns at the same time. Given the small number of such patients, this would not have influenced; the statistical analysis.

<H2>Organ involvement

Vascular involvement was defined as 1 of the following: presence and/or history of digital ulcers, confirmed pulmonary arterial hypertension defined as an increased mean pulmonary arterial pressure of 25 mm Hg or more on right-sided heart catheterization and a pulmonary capillary pressure no higher than 15 mm Hg and/or scleroderma renal crisis.

Cardiac involvement was defined as left ventricular ejection fraction dysfunction less than 55%, increased brain natriuretic peptide levels at least 300 pg/mL, or history of pericarditis.

Pulmonary involvement was defined as dyspnea grade III according to the New York Heart

Association classification, reduced diffusing capacity of carbon monoxide (< 80%), forced vital capacity less than 80%, and interstitial lung disease or lung fibrosis on computed tomography scans. Gastrointestinal involvement (esophageal gastrointestinal motility dysfunction with esophageal symptoms epigastralgia, or intestinal symptoms) and musculoskeletal involvement (synovitis, joint contractures, and creatine phosphokinase levels of 145 UI/L or higher) were also recorded.

<H2>Statistical analysis

Quantitative variables were expressed as means with standard deviation, or medians with interquartile range. Qualitative variables were presented as percentages. Comparison tests were performed by using chi-square analysis for qualitative variables (such as pigmentation patterns and characteristics of the patient's disease) or the Fisher exact test when needed. As quantitative variables do not fit with normal distribution according to the Shapiro-Wilk test, the nonparametric Mann-Whitney test was used for comparisons of such data. Multivariate analysis was performed to investigate independent factors associated with diffuse hyperpigmentation by using logistic regression with a backward stepwise procedure. All analyses were performed with Stata software (version 13.1, Stata Corp LP, College Station, TX). *P* values less than .05 were considered significant.

<H1>RESULTS

<H2>Demographic and clinical characteristics of enrolled patients

Patient characteristics are presented in Table I. The study included 239 patients (61 men and 178 women). The mean age was 59.7 years ($\sigma = 12.85$ years). A total of 169 patients (70.7%) were classified as having limited cutaneous systemic sclerosis and 70 (29.3%) were classified as having diffuse cutaneous SSc (DSSc). In all, 35 patients (14.6%) with SSc showed symptoms compatible with overlap syndrome. The mean modified Rodnan skin score (MRSS) was 9.4 ($\sigma = 9.8$).

The prevalence of skin pigmentation disorders in the cohort was 36.8% (88 of 239), with 58 and 35 patients developing skin hyperpigmentation and hypopigmentation, respectively. Of the patients with skin pigmentation disorders, 68.2% (60 of 88) had phototype II to III and 30.7% (27 of 88) had phototype IV to VI. No patients had phototype I. As shown in Table II, of the patients with pigmentation disorders, 34 (38.6%) presented with diffuse hyperpigmentation, 24 (27.3%) presented with hyperpigmentation limited to sun-exposed areas, 9 (10.2%) presented with hypopigmented flecked macules localized on the face (forehead), neck, and upper part of the chest and back, 11 (12.5%) presented with hypopigmented lesions located all over the body, and 15 (17%) presented with hypopigmented macules limited to the acral areas. A total of 5 patients had both significant hypopigmentation and hyperpigmentation. Of the patients with hyperpigmentation (of either diffuse or of sun-exposed areas), 40 (68.9%) reported a history of enhanced and prolonged tanning during summer.

<H2>Hyperpigmentation disorder is associated with DSSc

As shown in Tables I and II, a significantly higher proportion of patients with DSSc were associated with hyperpigmentation ($P = .003$) and, in particular, with diffuse hyperpigmentation ($P = .001$) compared with the proportion of patients without pigmentation disorders. Diffuse hyperpigmentation ($P = .001$) was significantly associated with an elevated MRSS and with the absence of anticentromere antibodies ($P = .004$).

<H2>Hyperpigmentation disorder is associated with digital ulcers in SSc

Having established a positive association between diffuse hyperpigmentation and DSSc, we wondered whether they could be associated with clinical features of SSc. We first observed that the duration of RP was shorter in patients with hyperpigmentation than in those without pigmentation disorder (mean duration, 10.3 ± 8.6 years versus 17.9 ± 13.3 years, respectively [$P = 10^{-4}$]). Likewise, onset of RP less than 10 years from the appearance of SSc

was significantly associated with hyperpigmentation ($P < 10^{-4}$). However, a similar analysis evaluating the association of pigmentation disorders and disease duration (with 2 stratifications: ≤ 5 years and > 5 years) indicated that it was not statistically significant (Table II).

As shown in Table III, we found a significant association between diffuse hyperpigmentation and the presence of digital ulcers ($P = .005$). Multivariate logistic regression analyses for patient characteristics associated with diffuse hyperpigmentation showed a significant positive association with vascular involvement (odds ratio, 2.96; 95% confidence interval, 1.28-6.89) and a negative association with RP evolving for more than 10 years (odds ratio, 0.28; 95% confidence interval, 0.11-0.70). However, when other variables were accounted for, diffuse hyperpigmentation was no longer associated with DSSc.

<H1>DISCUSSION

This single-center study based on a cohort of 239 patients with SSc is, to our knowledge, the first to address the complete description of skin pigmentation abnormalities associated with SSc and to analyze the relation between these symptoms and organ involvement in SSc. We established 5 patterns based on the type of pigmentation changes (hypopigmentation versus hyperpigmentation) and their localization. Salt-and-pepper appearance, which is the most described pigmentation abnormality in the literature, may be equated with our pattern termed *hypopigmentation of the face, neck, and/or chest*.

In a recent study, Solanki et al observed that salt-and-pepper appearance is related to DSSc.¹⁵ However, they failed to demonstrate any significant relation between skin pigmentation abnormalities and other symptoms of SSc. In our cohort, we observed that hyperpigmentation was associated not only with DSSc but also with a higher MRSS, a shorter duration of RP, and the absence of anticentromere antibodies, which are consistent with DSSc

characteristics. However, we could not confirm any significant association between hyperpigmentation and disease duration.

For the first time, to our knowledge, we have clearly demonstrated that diffuse hyperpigmentation is related to digital ulcers, which is symptom of vascular involvement in SSc. The pathogenesis of pigmentation disorders associated with SSc is still unclear. Recently, endothelin-1 (ET-1), which is a vasoconstrictive factor shown to be elevated in SSc and associated with vascular complications as digital ulcers,¹⁸⁻²⁰ could also act as a melanogenic factor and has been found to be elevated in the epidermis of patients with DSSc and hyperpigmentation.^{21,22} This suggests that ET-1 plays an important role in the pathogenesis of the skin hyperpigmentation associated with patients with SSc. Therefore, ET-1 could be the missing link between hyperpigmentation and digital ulcers and/or vascular involvement. Highlighting the relation between skin hyperpigmentation disorders and digital ulcers in SSc is of great interest because we have recently demonstrated that digital ulcers could be associated with increased risk of mortality in patients with SSc.²¹ These findings now need to be confirmed by larger community-based studies such as the European Scleroderma Trials and Research cohort.²²

Our study has some limitations. First, it was a retrospective study with a limited number of subjects included in each pattern, so it lacks power. This could explain why we did not find any significant association between pigmentation skin disorders and pulmonary arterial hypertension or renal crisis alone, as they constitute rare events. Second, the study was a single-center study and may not reflect the general SSc population, especially regarding skin phototype, as most of the patients were whites.

In conclusion, this study demonstrates a strong association between diffuse hyperpigmentation and digital ulcers. Screening for hyperpigmentation disorders could be useful in the management of patients with SSc, both as a diagnostic tool when faced with

early undifferentiated symptoms and as a marker to identify patients who are most at risk of developing digital ulcers and/or vascular involvement.

<ACK>We thank Professor Ray Cooke, director of the Department of Language and Culture, University of Bordeaux. for critical review of our manuscript.

REFERENCES

1. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology (Oxford)*. 2012;51(6):1017-1026.
doi:10.1093/rheumatology/ker269.
2. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010;69(10):1809-1815. doi:10.1136/ard.2009.114264.
3. Osler S. On diffuse scleroderma: with special reference to diagnosis, and to the use of the thyroid-gland extract. *Journal of Cutaneous Diseases*. 1898;16:49.
4. Tuffanelli DL, Winkelmann RK. Systemic scleroderma, a clinical study of 727 cases. *Arch Dermatol*. 1961;84:359-371.
5. Sharma VK, Trilokraj T, Khaitan BK, Krishna SM. Profile of systemic sclerosis in a tertiary care center in North India. *Indian J Dermatol Venereol Leprol*. 2006;72(6):416-420.
6. Reveille JD, Fischbach M, McNearney T, et al. Systemic sclerosis in 3 US ethnic groups: a comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. *Semin Arthritis Rheum*. 2001;30(5):332-346.
doi:10.1053/sarh.2001.20268.

7. Sanchez JL. Vitiligolike macules in systemic scleroderma. *Arch Dermatol*. 1983;119(2):129-133. doi:10.1001/archderm.119.2.129.
8. Jawitz JC, Albert MK, Nigra TP, Bunning RD. A new skin manifestation of progressive systemic sclerosis. *J Am Dermatol*. 1984;11(2 Pt 1):265-268.
9. Sukenik S, Kleiner-Baumgarten A, Horowitz J. Hyperpigmentation along tendons in progressive systemic sclerosis. *J Rheumatol*. 1986;13(2):474-475.
10. Fam AG, Lee P. The belt sign in scleroderma. *J Rheumatol*. 1990;17(5):725-726.
11. Ee HL, Tan SH. Reticulate hyperpigmented scleroderma: a new pigmentary manifestation. *Clin Exp Dermatol*. 2005;30(2):131-133. doi:10.1111/j.1365-2230.2004.01683.x.
12. Singh A, Ambujam S, Varghese A, Vishranth SP, Sadanandan N. Salt-and-pepper appearance: a cutaneous clue for the diagnosis of systemic sclerosis. *Indian J Dermatol*. 2012;57(5):412-413. doi:10.4103/0019-5154.100512.
13. Chuamanochan M, Haws AL, Pattanaprichakul P. Reticulate hyperpigmentation in systemic sclerosis: a case report and review of the literature. *J Med Case Rep*. 2015;9(1):459. doi:10.1186/s13256-015-0697-2.
14. Darrigade A-S, Védie AL, Gauthier C, et al. Pigmented skin patches without scleroderma as a predominant clinical symptom revealing systemic sclerosis. *Clin Exp Dermatol*. 2016;41(4):379-382. doi:10.1111/ced.12752.
15. Solanki KK, Hor C, Chang WSJ, Frampton C, White DHN. Clinical utility of hypo- and hyperpigmentation of skin in diffuse cutaneous systemic sclerosis. *Int J Rheum Dis*. 2017;20(6):767-773. doi:10.1111/1756-185X.13049.
16. Pope JE, Shum DT, Gottschalk R, Stevens A, McManus R. Increased pigmentation in scleroderma. *J Rheumatol*. 1996;23(11):1912-1916.

17. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2013;72:1747-1755. doi:10.1136/annrheumdis-2013-204424.
18. Vancheeswaran R, Magoulas T, Efrat G, et al. Circulating endothelin-1 levels in systemic sclerosis subsets--a marker of fibrosis or vascular dysfunction? *J Rheumatol*. 1994;21(10):1838-1844.
19. Yamane K, Miyauchi T, Suzuki N, et al. Significance of plasma endothelin-1 levels in patients with systemic sclerosis. *J Rheumatol*. 1992;19(10):1566-1571.
20. Kadono T, Kikuchi K, Sato S, Soma Y, Tamaki K, Takehara K. Elevated plasma endothelin levels in systemic sclerosis. *Arch Dermatol Res*. 1995;287(5):439-442.
21. Meunier P, Dequidt L, Barnetche T, et al. Increased risk of mortality in systemic sclerosis-associated digital ulcers: a systematic review and meta-analysis [e-pub ahead of print]. *J Eur Acad Dermatol Venereol*. doi:10.1111/jdv.15114, accessed
22. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis*. 2007;66(6):754-763. doi:10.1136/ard.2006.062901.

Fig 1. Hyperpigmentation patterns: diffuse hyperpigmentation (A) and hyperpigmentation localized on sun-exposed areas (B).

Fig 2. Hypopigmentation patterns: hypopigmentation located on the face, neck, and chest (A); hypopigmented lesions localized on acral areas (forearms, hands, lower legs, and feet) (B); and diffuse hypopigmented lesions located all over the body (C).

Table I. Demographic and clinical features of the study patients with SSc

Feature	Total	Pigmentation disorders		No pigmentation disorder
		Hyperpigmentation	Hypopigmentation	
Demographic features				
No.	239	58	35	151
Mean age, y (σ)	59.7 (12.8)	57.5 (11.8)	57.7 (12.7)	61.1 (13.2)
Ratio of males to females, n (%)	61 (25.5)/178 (74.5)	16 (27.6)/42 (72.4)	8 (22.9)/27 (77.1)	38 (25.2)/113 (74.8)
Clinical features				
Limited SSc-n(%)	169 (70.7)	32 (55.2)	22 (62.9)	118 (78.1)
Diffuse SSc-n(%)	70 (29.3)	26 (44.8)*	13 (37.1)	33 (21.9)
Overlap syndrome-n(%)	35 (14.6)	9 (15.5)	4 (11.4)	23 (15.2)
Mean time since onset of Raynaud phenomenon, y (σ)	16.1 (12.8)	10.3 (8.6)	17.9 (12.7)	17.9 (13.5)
Mean peak MRSS (σ)	9.4 (9.8)	12.9 (10.5)	13.5 (12.6)	7.3 (8.3)

MRSS, Modified Rodnan skin score; SSc, systemic sclerosis.

* $P < .01$ (statistically significant).

Table II. Associations between clinical pigmentation patterns and general and cutaneous features

Feature	Pigmentation disorders (n = 88 [36.8%])					No pigmentation disorder (n = 151 [63.2%])
	Hyperpigmentation		Hypopigmentation			
	Diffuse (n = 34 [38.6%])	Sun- exposed (n = 24 [27.3%])	Face, neck, and/or chest (n = 9 [10.2%])	Acral (n = 15 [17%])	Diffuse (n = 11 [12.5%])	
Subset of SSc						
DSSc, n (%)	17 (50)*	9 (37.5)	4 (44.4)	3 (20)	6 (54.6) [†]	33 (21.9)
LSSc, n (%)	17 (50)	15 (62.5)	5 (55.6)	12 (80)	5 (45.4)	118 (78.1)
Onset of pigmentation disorders, n (%)						
Before diagnosis	8 (23.5)	3 (12.5)	1 (11.1)	3 (20)	1 (9.1)	
At diagnosis	6 (17.6)	2 (8.3)	1 (11.1)	0	1 (9.1)	
After diagnosis	18 (52.9)	19 (79.2)	4 (44.4)	9 (60)	4 (36.4)	
Mean time (σ), mo	34.1 (20.25)	59.9 (54.8)	34 (36.7)	67.7 (103)	31.5 (22.6)	
Phototype						
I to III, n (%)	22 (64.7)	17 (70.8)	3 (33.3)	13 (86.7)	8 (72.7)	
IV to VI, n (%)	12 (35.3)	7 (29.2)	6 (66.7)	2 (13.3)	2 (18.2)	
Tanning easier, n (%)	23 (67.6)	17 (70.8)	2 (22.2)	5 (33.3)	6 (54.5)	19 (12.6)
Pruritus, ¹ n (%)	6 (17.6)	2 (8.3)	2 (22.2)	1 (6.7)	4 (36.4)	
Duration of RP						
≤10 y, n (%)	20 (58.8)*	15 (62.5)*	3 (33.3)	6 (40)	3 (27.3)	45 (29.8)
>10 y, n (%)	13 (38.2)	9 (37.5)	5 (55.6)	9 (60)	7 (36.6)	93 (61.6)
Disease duration since other symptoms						
≤5 y, n (%)	14 (41.2)	8 (33.3)	3 (33.3)	5 (33.3)	4 (36.3)	39 (25.8)
>5 y, n (%)	20 (58.8)	16 (66.7)	6 (66.7)	10 (66.7)	7 (63.6)	107 (70.9)
Peak MRSS, mean (σ)						
Mild (≤14)	20 (58.8)	17 (70.8)	5 (55.6)	12 (80)	5 (45.4)	123 (81.5)
Moderate (15-29)	8 (23.5)	5 (20.8)	2 (22.2)	2 (13.3)	2 (18.2)	15 (9.9)
Severe (≥30)	6 (17.6)*	0 (0)	1 (11.1)	0 (0)	4 (36.4)*	6 (4.0)
Autoantibodies, n (%)						
Anticentromeres,	8 (23.5)* ²	9 (37.5)	4 (44.4)	10 (66.7)	4 (36.4)	77 (51.0)
Antitopoisomerase I	10 (29.4)	7 (29.2)	2 (22.2)	2 (13.3)	4 (36.4)	27 (17.9)
RNA polymerase III	3 (8.8)	1 (4.2)	1 (11.1)	0 (0)	0 (0)	3 (1.9)

**P* < .01 (statistically significant).

[†]*P* < .05 (statistically significant).

DSSc, Diffuse systemic sclerosis; LSSc, limited systemic sclerosis; RP, Raynaud phenomenon; SSc, systemic sclerosis.

Table III. Associations between clinical pigmentation patterns and systemic features

Feature	Pigmentation disorders (n = 88 [36.8%])					No pigmentation disorder (n = 151 [63.2%])
	Hyperpigmentation		Face, neck, and/or chest (n = 9 [10.2%])	Hypopigmentation		
	Diffuse (n = 34 [38.6%])	Sun- exposed (n = 24 [27.3%])		Acral (n = 15 [17%])	Diffuse (n = 11 [12.5%])	
Vascular involvement, n (%)	23 (67.6)*	8 (33.3)	7 (77.8)	10 (66.7)	8 (72.7)	65 (43.0)
Digital ulcers, n (%)	21 (61.8)*	8 (33.3)	5 (55.6)	10 (66.7) [†]	7 (63.6)	54 (35.8)
PAH, n (%)	2 (5.9)	0 (0)	2 (22.2)	1 (6.7)	0 (0)	8 (5.3)
Scleroderma renal crisis, n (%)	3 (8.8)	0 (0)	1 (11.1)	0 (0)	1 (9.1)	5 (3.3)
Cardiac involvement, n (%)	8 (23.5)	1 (4.2)	4 (44.4) [†]	1 (6.7)	4 (36.4) [†]	18 (11.9)
Reduced LEVF, n (%)	3 (8.8)	0 (0)	2 (22.2)	0 (0)	0 (0)	8 (5.3)
Elevated BNP, n (%)	6 (17.6)	0 (0)	3 (33.3)	1 (6.7)	3 (27.3)	14 (9.3)
Pericarditis, n (%)	5 (14.7)*	1 (4.2)	2 (22.2) [†]	0 (0)	2 (18.2) [†]	2 (1.3)
Pulmonary involvement, n (%)	19 (55.9)	9 (37.5)	4 (44.4)	7 (46.7)	5 (45.4)	57 (37.7)
Dyspnea, n (%)	11 (32.3)	4 (16.7)	3 (33.3)	5 (33.3)	4 (36.4)	32 (21.2)
Reduced DLCO, n (%)	24 (70.6)	16 (66.6)	8 (88.9)	11 (73.3)	10 (90.9)	108 (71.5)
Restrictive syndrome, n (%)	6 (17.6)	5 (20.8)	2 (22.2)	3 (20.0)	2 (18.2)	39 (25.8)
Interstitial lung disease, n (%)	16 (47.1) [†]	7 (29.2)	4 (44.4)	4 (26.7)	4 (36.4)	43 (28.5)
Fibrosis, n (%)	5 (14.7)	3 (12.5)	2 (22.2)	2 (13.3)	2 (18.2)	21 (13.9)
Gastrointestinal involvement, n (%)	26 (76.5)	18 (75.0)	8 (88.9)	13 (86.7)	8 (72.7)	107 (70.9)
Esophageal symptoms, n (%)	25 (73.5)	18 (75.0)	8 (88.9)	13 (86.7)	8 (72.7)	103 (68.2)
Stomach symptoms, n (%)	5 (14.7)	2 (8.3)	3 (33.3)	3 (20.0)	1 (9.1)	23 (15.2)
Diarrhea, n (%)	4 (11.8)	4 (16.6)	1 (11.1)	3 (20.0)	2 (18.2)	25 (16.5)
Constipation, n (%)	5 (14.7)	1 (4.2)	1 (11.1)	5 (33.3) [†]	2 (18.2)	14 (9.3)
Musculoskeletal involvement, n (%)						
Synovitis	9 (26.5)	8 (33.3)	1 (11.1)	3 (20.0)	1 (9.1)	30 (19.9)

Comparisons were made between patients of each skin pigmentation pattern and patients without pigmentation disorder.

* $P < .01$ (statistically significant).

[†] $P < .05$ (statistically significant)

BNP, Brain natriuretic peptide; *DLCO*, diffusing capacity of carbon monoxide; *LEVF*, left ventricular ejection fraction; *PAH*, pulmonary arterial hypertension.

Abbreviations used:

DSSc: diffuse systemic sclerosis

ET-1: endothelinendothelin-1

MRSS: modified Rodnan skin score

RP: Raynaud phenomenon

SSc: systemic sclerosis

Figure 1

Hyperpigmentation

A

Diffuse

B

Sun-exposed

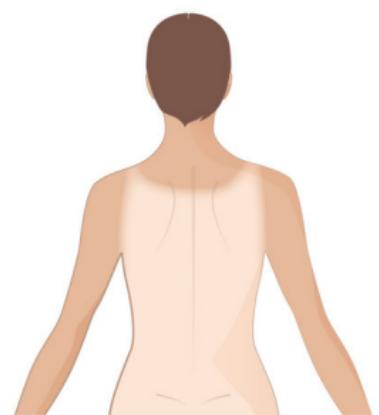
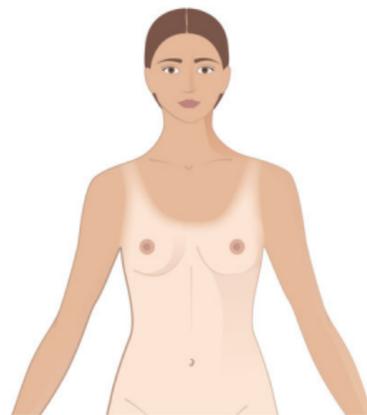
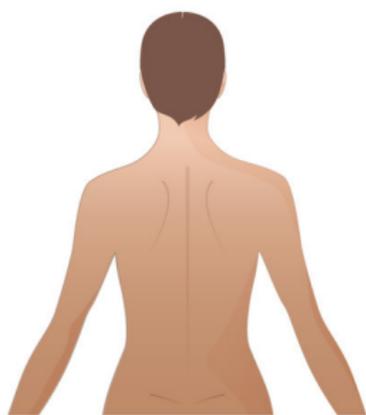
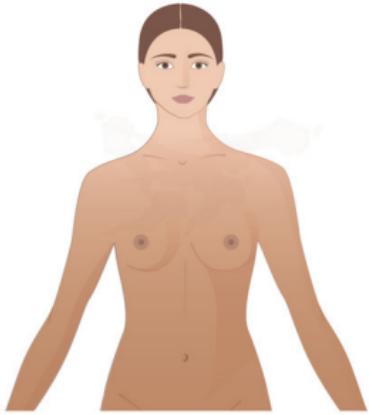


Figure 2

Hypopigmentation

A

Face/neck/chest



B

Acral



C

Diffuse

