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Les télangiectasies au cours de la sclérodermie systémique : distribution et associations clinico-biologiques

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AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

TABLES DES MATIERES

RESUME

Les télangiectasies au cours de la sclérodermie systémique : distribution et associations clinico-biologiques

Contexte : Les télangiectasies (TA), fréquentes au cours de la sclérodermie systémique (ScS), sont un critère de classification de la maladie, et pourraient être un marqueur clinique de la sévérité de la vasculopathie, notamment de l'hypertension artérielle pulmonaire (HTAP). Notre étude visait à décrire la distribution des TA sur l'ensemble du corps, puis à déterminer leur association avec les caractéristiques clinico-biologiques des patients ScS pour enfin préciser leur utilité dans l'identification des patients atteint d'HTAP.

Méthode : Les patients étaient inclus dans cette étude transversale s'ils validaient les critères ACR/EULAR 2013 de la ScS**.** Ceux ayant bénéficié d'un traitement par laser n'étaient pas inclus. Nous avons recueilli quantitativement les TA sur l'ensemble du corps, délimité en 16 zones corporelles. Les associations entre le nombre de TA et les caractéristiques clinico-biologiques étaient étudiées par régression linéaire en analyse univariée, ajustée puis multivariée.

Résultats : Nous avons inclus 106 patients de notre Centre de Référence National dont 12 ayant une HTAP. La répartition des TA était : 37,1% sur le visage, 33,2% sur les membres supérieurs dont 26,4% sur les mains, 28,1% sur le tronc dont 17,0% sur sa partie supérieure et 1,5% sur les membres inférieurs. En analyse multivariée, le nombre de TA était indépendamment associé à l'HTAP (p=0,038), l'embolie pulmonaire (p=0,012), l'endogline soluble (p=0,034), la diminution du débit de filtration glomérulaire (p=0,038) et le sexe masculin (p=0,033). Concernant l'identification de l'HTAP, les aires sous les courbes ROC du nombre de TA sur l'ensemble du corps, sur les mains, et à la

fois sur le visage et les mains étaient respectivement de 0,77(0,57-0,89), 0,77(0,57-0,88) et 0,81(0,57-0,91).

Conclusion : Chez les patients atteint de ScS, les TA sont principalement localisées sur le visage, les mains et la partie supérieure du tronc. Elles sont le témoin de la vasculopathie présente dans la maladie notamment pulmonaire et peuvent être utilisées comme marqueur clinique afin d'aider à l'identification des patients atteint d'HTAP.

INTRODUCTION

Systemic sclerosis (SSc) is a rare and severe connective tissue disease characterized by microvascular damage, specific immunologic abnormalities, and fibrosis of the skin and internal organs (1). Although fibrosis is the most prominent feature of SSc, the vascular abnormalities could be the earliest manifestation of the disease. SSc vasculopathy is caused by a major endothelial dysfunction, a defective angiogenesis and the activation of coagulation and platelets. Clinical symptoms of vascular involvement are mainly Raynaud's phenomenon, digital ulcers, scleroderma renal crisis or pulmonary arterial hypertension (PAH) (2). Telangiectasia (TA) could also be one of the vascular manifestation of SSc (3–8).

TA are formed by a dilatation of the post-capillary venules in the upper horizontal plexus of the skin (9). They are common in SSc and are included in the new American College of Rheumatology (ACR)/EUropean League Against Rheumatism (EULAR) 2013 Classification Criteria for SSc (1). Moreover, TA could also be associated with the presence of PAH in SSc and the recent DETECT algorithm has included TA as a risk factor for this complication (5,6,10). PAH occurs in approximately 8–12% of patients with SSc, and is one of the leading cause of morbimortality in this disease. Therefore, detecting PAH in its early phases to slow down the progression of the disease with adequate treatment is a major issue in SSc (11,12).

While some studies have addressed the issue of the association between TA and clinical manifestations of SSc, many questions are still not answered. While they are most commonly observed on the hands and face, they can be present on the whole body (3–8). However, no study has precisely described the total number and fine distribution of TA in SSc. Moreover, the clinical associations between TA observed on

the whole body is unknown. Finally, the precise biologic mechanisms causing the development of TA in SSc are still unknown. The role of angiogenic factors such as the Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor β (TGFβ) pathways, especially. endoglin (CD105) is not fully understood (13–15).

To address these issues, we designed this cross-sectional study to describe the total number, whole body distribution, and associations with clinical manifestations of TA in SSc. As we hypothesized that TA could reflect the vasculopathy in SSc, we especially focused on severe vascular manifestations including PAH and measure VEGF and endoglin serum (sEndoglin) levels.

METHODS

Population

We designed a cross-sectional study and recruited patients over 18 years old followed in the National Referral Centre for Rare Systemic And Autoimmune Diseases, from July 2016 to March 2017. They were included in the study if they fulfilled the 2013 American College of Rheumatology (ACR)/EUropean League Against Rheumatism (EULAR) classification criteria for SSc (1).

Patients with a history of laser therapy to reduce the number of TA were excluded.

The study was declared to the French “Commission Nationale de l’Informatique et des Libertés” and with current French legislation and was conducted in agreement with the Declaration of Helsinki.

Data collection

The number of TA (total and >5mm, measured using a template), and their distribution in different body areas including face (centro-facial area, temporo-frontal area, cheeks, lips and tongue), trunk (neck, thorax, abdomen, back and lower back), upper limbs (arms, forearms and hands), lower limbs (thighs, legs and feet) were recorded at inclusion. In addition to the total number of TA, we also calculated a TA score from a method previously applied: for each area, TA were scored as 0 if no TA was present, 1 if there were less than 10 TA, and 2 if 10 or more TA were counted (5).

A global clinical evaluation of patients was performed using a standardized Case Report Form, prospectively filled. Data were collected mostly on the day of inclusion

(n=77, 77.6%). The mean duration (± standard deviation) between data collection and inclusion was -18 (80) days. Data collection included:

- age, sex, and smoking history (yes/no),
- disease characteristics: disease duration since the date of the First Non Raynaud's Phenomenon symptom (FNRP), disease duration since inclusion, scleroderma classification according to Leroy's classification (limited and diffuse cutaneous form) (16), autoantibodies status (anti-centromere or ACA, anti-topoisomerase I or ATA and anti-RNA polymerase III or RNAIII antibodies), EUropean Scleroderma Trials and Research (EUSTAR) Activity score (17), Medsger severity score (18) and Health Assessment Questionnaire-Disability Index (HAQ-DI) (19),
- treatments (yes/no): corticosteroid, immunosuppressive (cyclophosphamide, mycophenolate mofetil, mycophenolate acid, azathioprine, methotrexate, anticalcineurin, D-penicillamin, antimalarial synthesis, polyvalent immunoglobulin, anti-CD20, anti-TNFα, or anti-IL6) and PAH (phosphodiesterase type 5 inhibitor, endothelin receptor antagonist, prostacyclin analogues, or guanylate cyclase inhibitor) treatments,
- cardio-pulmonary parameters: New York Heart Association (NYHA) functional score; 6-minute walk test (6MWT) performed as recommended by the American Thoracic Society (ATS) (20); interstitial lung disease (ILD) diagnosed on a chest high-resolution CT-scan and staged according to Goh's criteria (21); pulmonary function tests (PFT) with total forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), diffusing coefficient for carbon monoxide (KCO); N-terminal pro-brain natriuretic peptide (Nt-proBNP); pulmonary arterial hypertension (PAH) defined as hemodynamically-proven pre-capillary group 1

pulmonary hypertension by right heart catheterization (RHC) (22); transthoracic echocardiography (TTE) with left ventricular ejection fraction (LVEF), peak tricuspid regurgitation velocity (TRV), estimated systolic pulmonary artery pressure (sPAP) and right atrial area,

- skin parameters: modified Rodnan skin score (mRSS) (23); digital ulcers (DU) (history and/or presence during the clinical evaluation); Nailfold videocapillaroscopy (NVC) with determination of patterns of microangiopathy using Cutolo stages (early, active and late) (24),
- renal parameters: history of scleroderma renal crisis; glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease (MDRD) equation; urinary abnormalities (proteinuria and/or haematuria),
- vascular parameters: history of deep vein thrombosis, pulmonary embolism or arterial thrombosis (myocardial infarction, ischemic stroke, or acute limb ischemia),
- musculoskeletal parameters: joint symptoms (pain or swelling); muscle symptoms (pain or weakness),
- biological parameters: anemia defined by haemoglobin ≤13g/dL for male and ≤12g/dL for female gender; ferritin level; C-reactive protein (CRP) and uricemia.

Angiogenic factors

The serum levels of two angiogenic factors (VEGF and sEndoglin) were measured the day of inclusion. VEGF and sEndoglin were measured, respectively, by Human VEGF Quantikine ELISA and Human Endoglin / CD105 Quantikine ELISA Kit of R&DSystems®, according to the supplier's recommendations.

Statistical analyses

Characteristics of the population were described using mean ± standard deviation, or median (interquartile range) in case of non-normality, for quantitative variables, and number (percentage) for qualitative variables. Characteristics of patients with and without PAH were compared using Student *t*-tests, or Wilcoxon tests in case of non-normality, for quantitative variables, and Fisher's exact tests for qualitative variables.

The average distribution of TA for each body area was calculated (and graphically represented) by the ratio of the sum of the number of TA for each body area for all patients to the sum of the total number of TA for all patients.

Correlations between the number of TA for each body area (and the total number of TA) were calculated using Spearman's rank correlation coefficients and graphically represented using a correlogram.

To study the associations between the total number of TA as the dependent variable, and the characteristics of participants as the explanatory variables, we first log-transformed the total number of TA (natural logarithms of the number of TA + 1) to normalize the distribution of the dependent variable. Then we studied the associations using (i) univariate linear regressions, and (ii) adjusted linear regressions for age at inclusion, gender, smoking history, disease duration since inclusion, scleroderma classification, and autoantibody status (ACA, ATA, RNAIII). Finally, two multiple linear regression models were built in order to study the associations between the log-transformed number total of TA and (i) clinical (PAH, DU, GFR, deep vein thrombosis, pulmonary embolism, arterial thrombosis) vasculopathy parameters, (ii) clinical and biological (VEGF and sEndoglin) vasculopathy parameters. These models were also adjusted for age at inclusion, gender, smoking history, disease duration since inclusion,

scleroderma classification, and autoantibody status (ACA, ATA, RNAIII). The regression coefficients were expressed as the percentage change in TA number (95% confidence interval (CI)) per unit change in the explanatory variable. For this, they were back-transformed and converted to percentage change by multiplying with 100 and subtracting 100%. Regression diagnostics were performed.

Finally, receiver-operating characteristic (ROC) curves were plotted and the areas under the curve (AUC) were calculated to assess the ability to discriminate between participants with and without PAH of (i) the total number of TA, (ii) the TA score, (iii) the number of TA on hands and face, and (iv) the number of TA on hands. Optimal thresholds that maximized sensitivity and specificity were also calculated.

All statistical analyses were performed using R software, version 3.2.5 (25), using “Hmisc”, “corrplot”, and “ROCR” packages. The threshold for statistical significance was set to $p<0.05$.

RESULTS

Baseline characteristics

The study population comprised 106 patients (Table 1), with a minority of male (21.7%) and a majority of limited cutaneous SSc (72.6%). There were 12 (11.3%) patients with PAH, 51 (48.6%) with DU, 12 (13.3%) with calcinosis, 0 (0.0%) with renal crisis, 16 (15.1%) with deep vein thrombosis, 8 (7.5%) with pulmonary embolism and 12 (11.3%) with arterial thrombosis.

Compared to patients without PAH, patients with PAH presented with a higher Medsger severity score (median (IQR) = 7 (4) vs 4 (3), p=0.007), a higher proportion of dyspnea (NYHA) stage III-IV (83.3% vs 24.5%, p<0.001), a lower 6'WT (350 ± 51m vs 439 ± 94.8m, p=0.004), a higher proportion of KCO <60% predicted (90.9% vs 13.5%, p<0.001), a higher proportion of Nt-proBNP >300ng/L (58.3% vs 16.3%, p=0.003), a higher sPAP (median (IQR) = 63.5 (25.7) vs 29 (10) mmHg, p<0.001) and a higher surface of right atrial (20.4 ± 5.7cm^2 vs 14.8 ± 3.7cm^2, p<001). They had also a more altered GFR (69.2 ± 14.3ml/mn/1.73m^2 vs 88.2 ± 21.5ml/mn/1.73m^2; p=0.004).

Table 1. Baseline characteristics, n=106

Variables	n (n PAH+)	Whole population	PAH+	PAH-	p
Age, years	106 (12)	60.6 ± 13.5	61.4 ± 10.2	60.5 ± 13.9	0.823
Male gender	106 (12)	23 (21.7)	0 (0.0)	23 (24.5)	0.065
Smoking history	106 (12)	45 (42.4)	3 (25.0)	42 (44.7)	0.230
Telangiectasias					
Total number *	106 (12)	30.0 (82.7)	122.5 (111.7)	28.0 (64.0)	**0.002**
Total number >5mm *	106 (12)	1.0 (5.0)	3.5 (6.2)	0.5 (4.7)	0.246
Score *	106 (12)	5.0 (6.0)	8.0 (2.5)	5.0 (5.0)	**0.009**
Disease characteristics					
Disease duration since FNRP, years	94 (10)	9.6 ± 7.5	11.9 ± 6.9	9.3 ± 7.6	0.300
Disease duration since inclusion, years	106 (12)	9.0 ± 7.4	12.3 ± 6.8	8.6 ± 7.5	0.109
Scleroderma classification					
Limited	106 (12)	77 (72.6)	11 (91.7)	66 (70.2)	0.173
Diffuse	106 (12)	29 (27.4)	1 (8.3)	28 (29.8)	0.173
Autoantibodies status					
ACA	105 (12)	55 (52.4)	10 (83.3)	45 (48.4)	**0.030**
ATA	105 (12)	22 (20.9)	1 (8.3)	21 (22.6)	0.450
RNAIII	105 (12)	4 (3.8)	0 (0.0)	4 (4.3)	-
Disease activity and severity					
EUSTAR Activity score *	94 (11)	1.0 (2.0)	2.0 (1.2)	0.5 (1.7)	0.070
Medsger Severity score *	87 (9)	4.0 (4.0)	7.0 (4.0)	4.0 (3.0)	**0.007**
HAQ-DI score	76 (8)	0.8 ± 0.7	1.0 ± 0.6	0.7 ± 0.7	0.268
Treatments					
Corticosteroids	106 (12)	39 (36.8)	1 (8.3)	38 (40.4)	0.052
Immunosuppressive therapy	106 (12)	36 (34.0)	2 (16.7)	34 (36.2)	0.215
PAH treatment	106 (12)	15 (14.2)	10 (83.3)	5 (5.3)	**<0.001**
Cardio-pulmonary parameters					
Dyspnea (NYHA)					
Stages I-II	106 (12)	73 (68.9)	2 (16.7)	71 (75.5)	**<0.001**
Stages III-IV	106 (12)	33 (31.2)	10 (83.3)	23 (24.5)	**<0.001**
6'WT, meters	95 (10)	429.6 ± 95.0	350.0 ± 51.0	439.0 ± 94.8	**0.004**
Presence of ILD	102 (12)	51 (50.0)	5 (41.7)	46 (51.1)	0.760
FVC <70% predicted	103 (11)	12 (11.7)	2 (18.2)	10 (10.9)	0.613
DLCO <60% predicted	101 (11)	40 (39.6)	11 (100.0)	29 (32.2)	**<0.001**
KCO <60% predicted	100 (11)	22 (22.0)	10 (90.9)	12 (13.5)	**<0.001**
Right axis deviation on ECG	101 (11)	6 (5.9)	2 (18.2)	4 (4.5)	0.127
Nt-proBNP >300ng/l	104 (12)	22 (21.2)	7 (58.3)	15 (16.3)	**0.003**
LVEF, %	100 (11)	62.9 ± 6.3	63.6 ± 5.4	62.8 ± 6.4	0.666
sPAP, mmHg *	89 (12)	30.0 (11.0)	63.5 (25.7)	29.0 (10.0)	**<0.001**
TRV, m/s *	93 (12)	2.6 (0.5)	3.9 (0.6)	2.5 (0.4)	**<0.001**
Surface of right atrium, cm^2	70 (10)	15.6 ± 4.4	20.4 ± 5.7	14.8 ± 3.7	**<0.001**
Skin parameters					
mRSS *	105 (12)	4.0 (5.0)	2.5 (3.3)	4.0 (6.0)	0.366

Digital ulcers	105 (12)	51 (48.6)	7 (58.3)	44 (47.3)	0.549
Calcinosis	90 (7)	12 (13.3)	2 (28.6)	10 (12.0)	0.234
Capillaroscopy (Stages of Cutolo)	40 (1)				
Normal		4 (10.0)	0 (0.0)	4 (10.3)	-
Early		7 (17.5)	0 (0.0)	7 (17.9)	-
Active		17 (42.5)	1 (100.0)	16 (41.0)	-
Late		12 (30)	0 (0.0)	12 (30.7)	-
Renal parameters					
Renal crisis	106 (12)	0 (0.0)	-	-	-
GFR, ml/mn/1.73m^2 (MDRD)	106 (12)	86.0 ± 21.6	69.2 ± 14.3	88.2 ± 21.5	**0.004**
Urinary abnormalities	95 (12)	16 (16.8)	2 (16.7)	14 (16.9)	1.000
Vascular parameters					
Deep vein thrombosis	106 (12)	16 (15.1)	4 (33.3)	12 (12.8)	0.081
Pulmonary embolism	106 (12)	8 (7.5)	2 (16.7)	6 (6.4)	0.224
Arterial thrombosis	106 (12)	12 (11.3)	1 (8.3)	11 (11.7)	1.000
Musculoskeletal parameters					
Joint symptoms	106 (12)	41 (38.7)	1 (8.3)	40 (42.5)	**0.026**
Muscular symptoms	105 (11)	22 (20.9)	0 (0.0)	22 (23.4)	0.115
Biological parameters					
Anemia	103 (12)	18 (17.5)	3 (25.0)	15 (16.5)	0.436
Ferritin, ng/ml	106 (12)	121.1 ± 157.6	67.8 ± 53.5	127.9 ± 165.2	0.215
CRP, mg/l	105 (12)	3.4 ± 3.4	3.9 ± 3.9	3.3 ± 3.4	0.548
Uricemia, mg/l	104 (11)	48.8 ± 14.3	58.0 ± 22.0	47.7 ± 12.8	**0.022**
Angiogenic factors					
VEGF, pg/ml	104 (12)	391.2 ± 232.6	445.3 ± 176.0	384.1 ± 238.9	0.394
sEndoglin, ng/ml	103 (12)	5.8 ± 1.3	6.1 ± 1.5	5.8 ± 1.3	0.450

Quantitative variables are expressed as mean ± standard deviation or median (interquartile range) (*). Qualitative variables are expressed as n (%).

SSc: systemic sclerosis; FNRP: first non-Raynaud's phenomenon symptom; PAH: pulmonary arterial hypertension; PAH+: patients with PAH; PAH-: patients without PAH; ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; RNAIII: anti-RNA polymerase III antibody; EUSTAR score: EUropean Scleroderma Trials and Research group's score; HAQ-DI: Health Assessment Questionnaire Disability Index; CRP: C-Reactive Protein; NYHA: New York Heart Association; 6'WT: six minutes' walk test; ILD: interstitial lung disease; FVC: forced vital capacity; mRSS: modified Rodnan skin score; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: diffusing coefficient for carbon monoxide; ECG: electrocardiography; Nt-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection function; sPAP: systolic pulmonary artery pressure; TRV: tricuspid regurgitation velocity; GFR: glomerular filtration rate; VEGF: vascular endothelial growth factor; sEndoglin: soluble endoglin.

Distribution of telangiectasias

Ninety-eight patients (92.5%) had at least one TA, including 55 (51.9%) with at least one TA >5mm. The median (IQR) number of TA, TA >5mm and TA score was respectively, 30 (82.7), 1 (5) and 5 (6) (Table 1).

The distribution of TA was: 37.2% on the face, 33.2% on the upper limbs including 26.4% on the hands, 28.1% on the trunk including 17.1% for the upper part of the trunk, and 1.5% on the lower limbs (Figure 1).

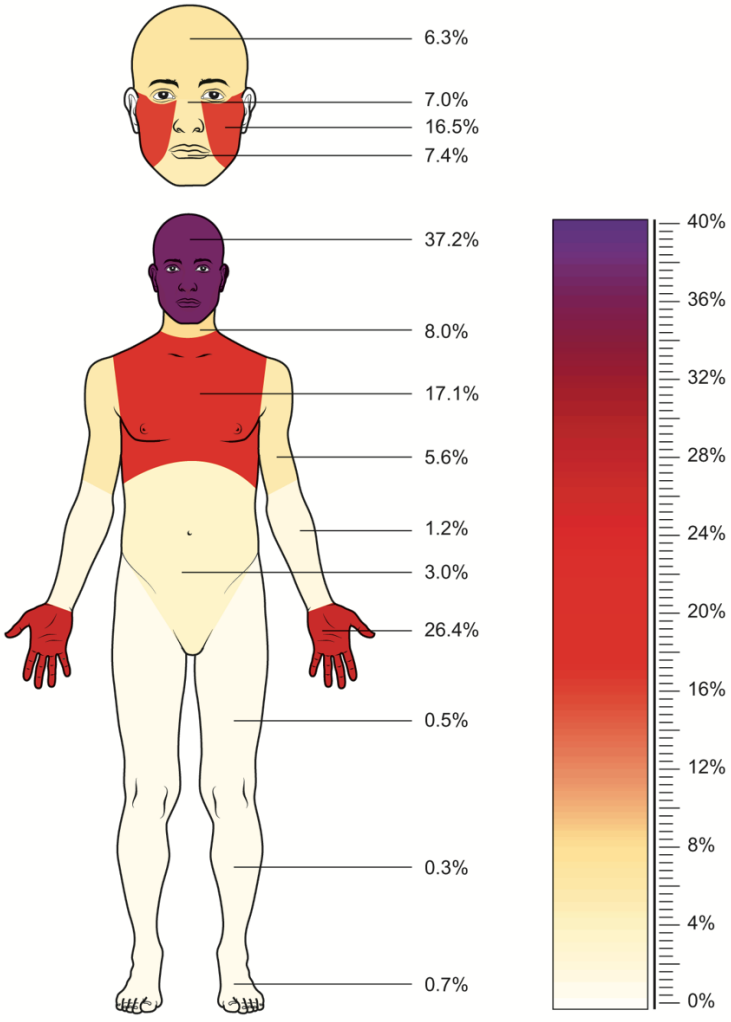

Figure 1: Distribution of telangiectasias for each body area

Results are expressed as the ratio of the sum of the number of telangiectasias for each body area for all patients to the sum of the total number of telangiectasias for all patients.

We found a positive and significant correlation between the total number of TA on the whole body and TA on the face (r=0.89, p<0.001), on the upper limbs (r=0.87, p<0.001), and on the hands (r=0.77, p<0.001) (Figure 2).

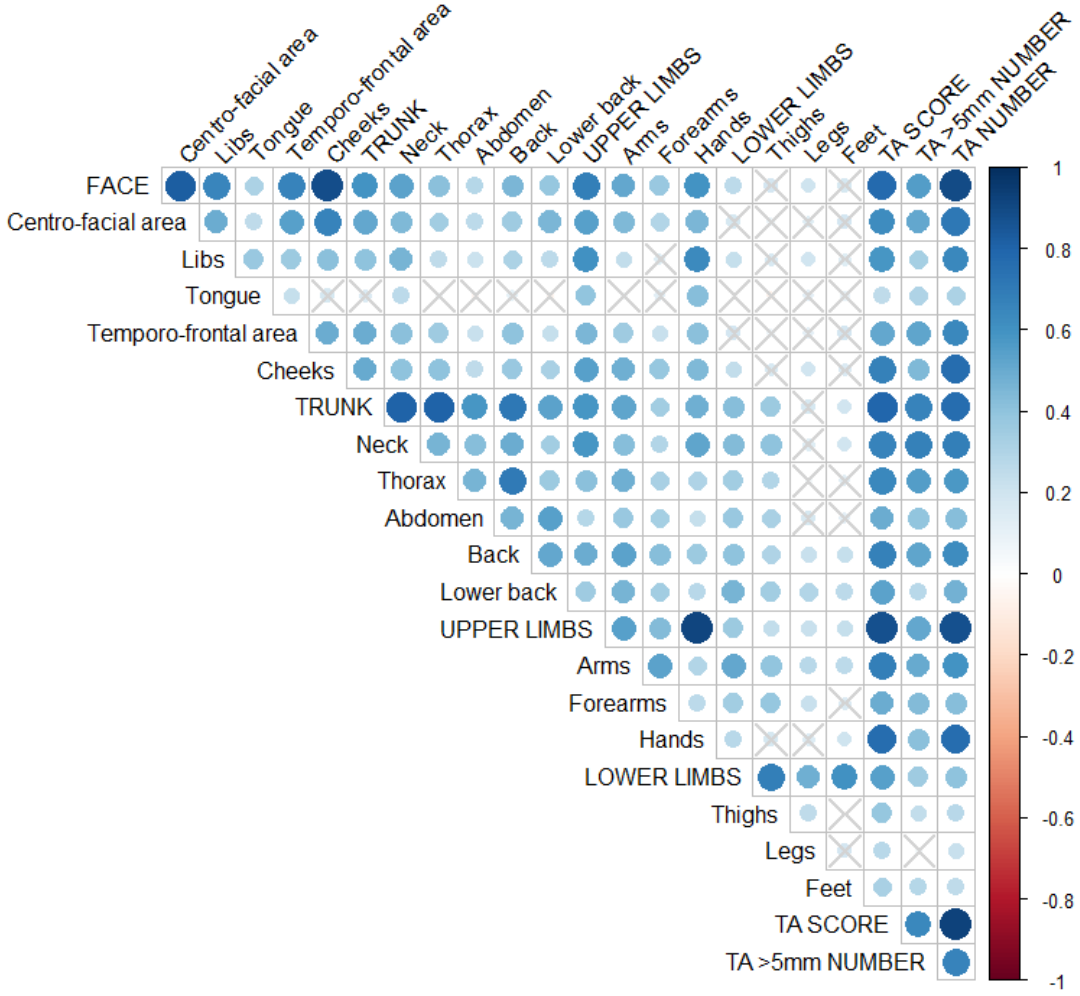

Figure 2: Correlogram representing the correlations between the number of telangiectasias for each body area (and the total number of telangiectasias)

Results are expressed as Spearman's rank correlation coefficients using a color scale. The grey “X” means that the coefficient is not significant.

Associations between the number of telangiectasias and characteristics of patients

The total number of TA was positively and significantly associated with the disease duration since the date of the FNRP (p=0.034), EUSTAR Activity score (p=0.033), Medsger Severity Score (p=0.038) in adjusted analyses (Table 2). Significant associations were also observed with PAH (p=0.005), KCO <60% predicted (p=0.021), increase in sPAP (p=0.045), active and late NVC patterns (p=0.004 and p=0.009, respectively) and pulmonary embolism (p=0.029) in adjusted analyses. We also found an association with dyspnea stage III-IV (p=0.045), 6'WT ≥median (p=0.016) and NT-proBNP >300ng/l (p=0.046) but only in non-adjusted analyses. Finally, we observed significant associations with increased CRP (p=0.026) and increased sEndoglin (p=0.044) in adjusted analyses. Conversely, there was no association between the total number of TA and the serum level of VEGF.

Table 2. Associations between the number of telangiectasias and the clinical characteristics of patients

Variables	Crude percentage change in TA number (CI95%)	p	Adjusted percentage change in TA number * (CI95%)	p
Age, per 1-year inc	1.9 (-0.2; 4.1)	0.086	1.3 (-0.9; 3.6)	0.242
Male gender	74.3 (-13.7; 251.9)	0.124	92.1 (-14.2; 330.5)	0.116
Smoking history (yes vs. no)	19.6 (-33.8; 116.0)	0.555	16.3 (-39.6; 124.0)	0.653
Disease characteristics				
Disease duration since FNRP, per 1-year inc	4.3 (0.2; 8.6)	**0.041**	5.0 (0.4; 9.8)	**0.034**
Disease duration since inclusion, per 1-year inc	5.4 (1.5; 9.5)	**0.007**	6.0 (1.5; 10.6)	**0.010**
Scleroderma classification (dcSSc vs lcSSc)	24.2 (-35.5; 139.3)	0.519	103.6 (-15.4; 389.9)	0.116
Autoantibodies status				
ACA	23.3 (-31.6; 122.2)	0.487	97.5 (-7.3; 320.7)	0.081
ATA	20.4 (-41.6; 148.2)	0.616	35.5 (-44.8; 232.9)	0.509
RNAIII	-22.5 (-83.4; 261.4)	0.746	4.9 (-80.0; 450.5)	0.955
Disease activity and severity:				
EUSTAR Activity score ≥ median (1)	112.4 (12.3; 302.0)	**0.022**	101.0 (7.1; 277.3)	**0.033**
Medsger Severity score ≥ median	111.2 (10.7; 302.7)	**0.025**	124.2 (5.7; 375.5)	**0.038**
HAQ-DI score, per 1-point inc	-0.6 (-40.0; 64.7)	0.981	17.3 (-36.3; 115.8)	0.610
Treatments				
Corticosteroids	8.2 (-41.0; 98.6)	0.800	67.7 (-20.6; 254.0)	0.179
Immunosuppressive	22.6 (-33.9; 127.3)	0.518	59.8 (-18.4; 213.2)	0.175
PAH treatment	164.3 (16.5; 499.9)	**0.022**	167.3 (19.8; 496.0)	**0.018**
Cardio-pulmonary parameters				
PAH	268.4 (51.3; 797.3)	**0.004**	265.4 (52.4; 776.2)	**0.005**
Dyspnea Stage III-IV vs I-II (NYHA)	89.7 (2.0; 252.9)	**0.045**	85.2 (-0.2; 243.4)	0.054
6'WT ≥ median (432.7m)	-53.2 (-74.5; -14.1)	**0.016**	-49.7 (-75.8; 4.4)	0.068
Presence of ILD	29.5 (-28.7; 135.3)	0.398	67.9 (-15.3; 232.7)	0.141
FVC < 70% predicted	16.9 (-53.9; 196.2)	0.742	8.3 (-61.8; 207.3)	0.881
DLCO < 60% predicted	141.0 (33.2; 336.0)	**0.004**	105.6 (11.9; 227.9)	**0.023**
KCO < 60% predicted	190.3 (43.3; 488.1)	**0.004**	137.8 (15.6; 389.3)	**0.021**
Right deviation axis on ECG	176.8 (-18.6; 841.0)	0.106	198.0 (-8.2; 867.6)	0.072
Nt-proBNP > 300 ng/l	108.2 (2.1; 324.4)	**0.046**	44.9 (-32.0; 208.9)	0.340
LVEF, per 1% inc	-1.5 (-6.1; 3.3)	0.533	-0.6 (-5.3; 4.3)	0.810
sPAP, per 1mmHg inc	2.4 (0.6; 4.2)	**0.010**	1,9 (0.1; 3.9)	**0.045**
TRV, per 1m/s inc	108.5 (32.3; 228.6)	**0.002**	80.7 (11.5; 192.8)	**0.019**
Surface of right atrium, per 1 cm^2 inc	7.7 (-0.5; 16.6)	0.072	6.5 (-1.8; 15.6)	0.133
Skin parameters				
mRSS ≥ median	39.9 (-22.2; 151.6)	0.264	14.7 (-42.1; 127.1)	0.695
Digital ulcers	30.5 (-27.6; 135.3)	0.378	5.6 (-43.7; 98.4)	0.865
Calcinosis	69.7 (-29.3; 307.6)	0.239	9.6 (-55.5; 170.1)	0.842
Capillaroscopy (Stages of Cutolo)				
Normal	-		-	
Early	28.4 (-76.4; 599.8)	0.774	91.3 (-70.1; 1123.7)	0.499

Active	1054.5 (156.7; 5091.3)	**<0.001**	1601.5 (189.1; 9914.7)	**0.004**
Late	1182.5 (169.0; 6014.4)	**0.002**	1744.3 (140.1; 14063.7)	**0.009**
Renal parameters				
GFR, per 1ml/mn/1.73m^2 (MDRD)	1.3 (-2.6; 0,0)	0.051	-1.2 (-2.5; 0.2)	0.109
Urinary abnormalities	1,9 (-27.3; 275.7)	0.233	21.0 (-47.8; 180.5)	0.657
Vascular parameters				
Deep vein thrombosis	52.1 (-32.6; 243.4)	0.315	61.7 (-27.2; 259.0)	0.241
Pulmonary embolism	386.7 (67.5; 1314.3)	**0.004**	240.0 (15.2; 904.1)	**0.029**
Arterial thrombosis	-10.5 (-64.5; 125.6)	0.815	-19.6 (-67.6; 99.6)	0.640
Musculoskeletal parameters				
Joint symptoms	28.7 (-29.3; 134.5)	0.410	10.8 (-39.1; 101.9)	0.737
Muscular symptoms	10.9 (-46.1; 127.9)	0.779	-7.0 (-53.8; 87.4)	0.840
Biological parameters				
Anemia	62.2 (-24.4; 248.3)	0.217	44.0 (-37.3; 230.9)	0.392
Ferritin, per 1ng/ml inc	0.0 (-0.2; 0.2)	0.983	0.0 (-0.2; 0.2)	0.554
CRP, per 1mg/l inc	10.7 (1.8; 20.4)	**0.018**	10.4 (1.3; 20.3)	**0.026**
Uricemia, per 1mg/l inc	1.7 (-0.4; 3.8)	0.112	1.0 (-1.0; 3.1)	0.323
Angiogenic factors				
VEGF, per 1pg/ml inc	0.0 (-0.1; 0.2)	0.496	0.0 (-0.1; 0.2)	0.691
sEndoglin, per 1ng/ml inc	29.3 (2.7; 62.8)	**0.030**	28.7 (1.0; 64.0)	**0.044**

* Associations adjusted for: age at inclusion, gender, smoking history, disease duration since inclusion, scleroderma classification, and autoantibody status (ACA, ATA, RNAIII).

inc: increase; dcSSc: diffuse cutaneous form of systemic sclerosis; lcSSc: limited cutaneous form of systemic sclerosis; FNRP: first non-Raynaud's phenomenon symptom; PAH: pulmonary arterial hypertension; ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; RNAIII: anti-RNA polymerase III antibody; EUSTAR score: EUropean Scleroderma Trials and Research group's score; HAQ-DI: Health Assessment Questionnaire Disability Index; CRP: C-Reactive Protein; NYHA: New York Heart Association; 6'WT: six minutes' walk test; ILD: interstitial lung disease; FVC: forced vital capacity; mRSS: modified Rodnan skin score; DLCO: Diffusing capacity of the lung for carbon monoxide; KCO: diffusing coefficient for carbon monoxide; ECG: electrocardiography; Nt-proBNP: N-terminal pro-brain natriuretic peptide; LVEF: left ventricular ejection function; sPAP: systolic pulmonary artery pressure; TRV: tricuspid regurgitation velocity; GFR: glomerular filtration rate; VEGF: vascular endothelial growth factor; sEndoglin: soluble endoglin.

The multivariate model including clinical and biological markers of vasculopathy revealed that the total number of TA was independently associated with male gender (percentage change (95% CI) = +144.4% (7.5; 455.9), p=0.033), PAH (+162.8% (5.6; 553.8), p=0.038), pulmonary embolism (+336.4% (39.0; 1270.1), p=0.012), decreased GFR (-1.6% (-3.2; -0.1) per 1ml/mn/1.73m^2 increase, p=0.038) and sEndoglin (+28.2% (1.2; 62.5), p=0.039) per 1ng/ml increase (Table 3).

Table 3. Multivariate analyses assessing the association between the number of telangiectasias and clinical and biological markers reflecting vasculopathy.

	Clinical markers*, n=105		Clinical and biological markers**, n=101	
	Percentage change in TA number (95% CI)	p	Percentage change in TA number (95% CI)	p
Age, per 1-year inc	0.9 (-1.5; 3.3)	0.467	1.3 (-1.1; 3.8)	0.279
Male gender	116.6 (-3.1; 384.1)	0.059	144.4 (7.5; 455.9)	**0.033**
Smoking history (yes vs. no)	42.3 (-26.6; 175.7)	0.293	53.9 (-20.6; 198.7)	0.199
Disease characteristics				
Disease duration since inclusion, per 1 year inc	4.3 (-0.1; 8.9)	0.056	3.8 (-0.7; 8.4)	0.097
Scleroderma classification (dcSSc vs lcSSc)	62.3 (-32.4; 289.6)	0.274	74.7 (-26.3; 314.4)	0.202
Autoantibodies status				
ACA	67.4 (-21.5; 257.1)	0.179	69.4 (-22.4; 269.7)	0.183
ATA	28.2 (-47.8; 215.1)	0.584	59.3 (-35.3; 292.3)	0.306
RNAIII	6.6 (-79.1; 443.7)	0.938	96.7 (-67.4; 1088.6)	0.456
Vasculopathy parameters				
PAH	178.6 (9.6; 608.0)	**0.031**	162.8 (5.6; 553.8)	**0.038**
Digital ulcers	28.8 (-46.5; 210.5)	0.569	28.1 (-46.5; 207.0)	0.574
GFR, per 1ml/mn/1.73m^2 inc	-1.2 (-2.6; 0.3)	0.123	-1.6 (-3.2; -0.1)	**0.038**
Deep vein thrombosis	-19.6 (-66.2; 91.0)	0.617	-16.9 (-64.3; 93.5)	0.664
Pulmonary embolism	304.8 (27.1; 1189.3)	**0.018**	336.4 (39.0; 1270.1)	**0.012**
Arterial thrombosis	-10.5 (-63.3; 118.3)	0.805	-9.7 (-62.2; 115.4)	0.815
Angiogenic factors				
VEGF, per 1pg/ml inc	-	-	0.1 (-0.1; 0.2)	0.359
sEndoglin, per 1ng/ml inc	-	-	28.2 (1.2; 62.5)	**0.039**

1 observation (*) and 5 observations (**) deleted due to missingness.

inc: increase; dcSSc: diffuse cutaneous form of systemic sclerosis; lcSSc: limited cutaneous form of systemic sclerosis; ACA: anti centromere antibody; ATA: anti topoisomerase I antibody; RNAIII: anti RNA polymerase III antibody; PAH: pulmonary arterial hypertension; GFR: glomerular filtration rate; VEGF: vascular endothelial growth factor; sEndoglin: soluble endoglin.

Telangiectasias as a discriminant marker of pulmonary arterial hypertension

The ROC analyses assessing the ability to discriminate the presence of PAH revealed that the AUC was significant and similar for the number of TA on the whole body (0.77 (0.57; 0.88)), on the hands (0.77 (0.57; 0.89)), on the hands and face (0.81 (0.57; 0.91)), as well as for the TA score (0.73 (0.56; 0.83)) (Figure 3).

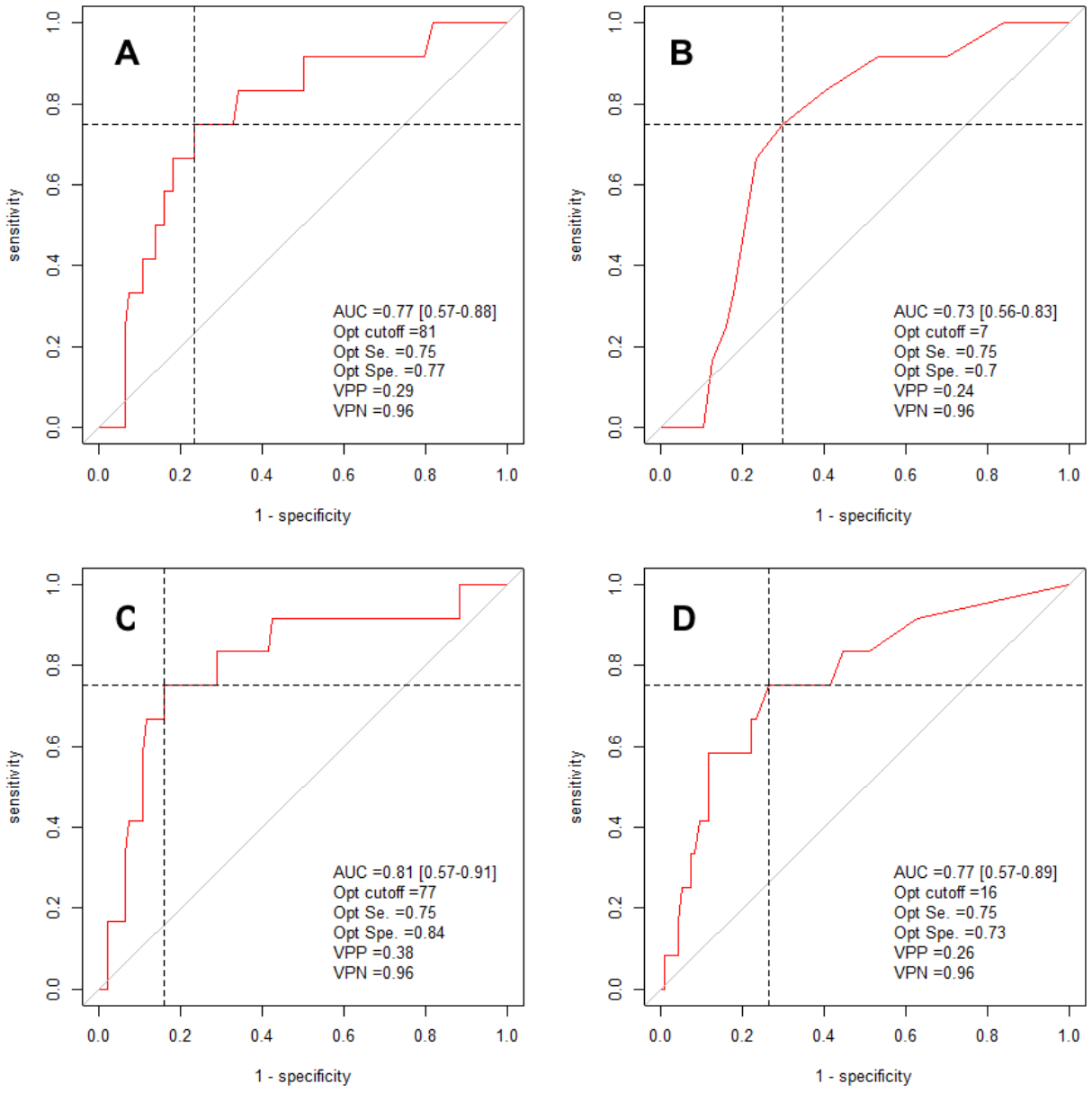

Figure 3: ROC curves assessing the ability to discriminate the presence of PAH for (A) the total number of TA on the whole body, (B) TA score, (C) the number of TA on hands and face, (D) and the number of TA on hands.

DISCUSSION

This study aimed to describe the whole skin distribution of TA in SSc-patients and assess the associations with clinical and biological manifestations with a focus on vascular characteristics. The main results are as follow: (i) the median (IQR) number of TA was 30 (82.7) and TA were mostly distributed on the face, hands and upper part of the trunk; (ii) male gender, PAH, pulmonary embolism, decreased GFR and sEndoglin were independently associated with the total number of TA; (iii) TA on the hands and/or face was well correlated with the total number of TA and could be useful to detect SSc-patients for PAH.

Distribution of telangiectasias

In our study, the median (IQR) number of TA was 30 (82.7) and 92.5% of SSc-patients had at least one TA. TA were mostly distributed on the face, hands and upper part of the trunk (Figure 1). These results have not been previously and precisely described in SSc. Some studied have suggested that TA were mostly distributed on the ventral surface of the digits (3,4,26). Interestingly, we show that the total number of TA was well correlated with the number of TA on the hands and/or face. This is meaningful as a thorough assessment of TA on the whole body is time consuming and our study suggest that a simple count on hands and/or face could be sufficient to have a good representation of the total number of TA. There is no clear explanation why TA are preferentially found in these areas. One hypothesis could be that the nature of the endothelium of the microvasculature of these sites could be different. Indeed, endothelial cell phenotypes vary between different organs, between different segments

of the vascular loop within the same organ, and between neighboring endothelial cells of the same organ and blood vessel type (27).

Associations between the number of telangiectasias and characteristics of patients

In this study, we observed relationships between the number of TA and several vasculopathy features (active/late NVC patterns, PAH, pulmonary embolism, decreased GFR and sEndoglin), but not with others (DU, calcinosis, and VEGF).

The association between TA and DU, skin fibrosis and calcinosis yielded discrepant results (4–8,28). These discrepancies could be explained by populations of different ethnicities, different prevalence of TA, different methods of TA collection and the use of composite criteria between studies.

The most important and severe vascular complication of SSc, namely PAH, was independently associated with the number of TA (but not TA >5mm). In the literature, this association has already been described using different methods of TA collection and PAH definitions (TTE and RHC) (4,5,7). A recent study found an association between prevalence of TA >5mm on the hands and the face and PAH (6). In addition, we and others have also shown an association between TA and higher dyspnea, Nt-proBNP and sPAP, and with the lower 6'WT and KCO (5,7,29). These can be easily explained by the association between PAH and these parameters. To go further in the assessment of TA and PAH, we assessed the potential for use in clinical practice of the number of TA on the hands and/or face to identify patients with current PAH. Using ROC curves, we found that the number of TA on the hands and/or face could be moderately effective to discriminate patients with PAH. The number of TA on the hands and the face seemed more effective in identifying patients with PAH. However, counting

the number of TA only on the hands is more practical in clinical practice. Of course, no causative role can be drawn from a cross-sectional study and further prospective studies are necessary to determine if the number of TA may serve as an early clinical biomarker for the development of PAH.

Concerning the other vascular manifestations, we found a positive association between TA and active/late NVC patterns. This is in line with many studies and is an evidence that TA reflects the severity of vasculopathy (6,29,30).

In our study, the total number of TA was also independently associated with pulmonary embolism, but not with other venous or arterial thrombosis. Several studies have shown an increased risk of venous thrombosis in SSc-patients compared to healthy controls, but none of them described a sub-population with a higher risk (31–34). There is no clear explanation for this association. We could suggest that TA, as a marker of vasculopathy, could reflect the widespread endothelial dysfunction in SSc. Endothelial dysfunction could be a trigger to thrombotic deposition by causing the loss of endothelial antithrombotic properties (2,35). The association found only with pulmonary embolisms and not with other venous or arterial thrombosis in our study could suggest that the endothelial dysfunction could be more important in pulmonary vessels in SSc-patients. Interestingly, we found a positive association between TA and CRP. Some studies have shown that venous endothelial dysfunction and venous thrombosis events were associated with the increase in baseline high-sensitivity C-reactive protein (36,37).

The number of TA was also independently associated with the decreased of GFR in patients without current or history of renal crisis, but we found no association with urinary abnormalities. To our knowledge, this has not been previously reported. Only one study has assessed an association between TA and GFR but the results were

negative (5). The main hypothesis is that the number of TA could be reflect microvascular involvement affecting the kidney.

In our study, the number of TA was independently associated with sEndoglin, which was consistent with two other studies (5,38). sEndoglin is a biomarker of various vascular pathologies, including SSc, related to endothelial dysfunction and membrane endoglin expression (39,15). Increased sEndoglin has been reported in SSc-patients with vasculopathy features, especially in patients with elevated sPAP (38,40). sEndoglin could act as an antagonist by interacting with TGFβ pathway, which might result in endothelial function impairment (41). This antagonistic effect could mimic the clinical phenotype of hereditary hemorrhagic telangiectasia type 1, an autosomal dominant disorder due to an inhibitory mutation of endoglin gene, and characterized by multiple cutaneous-mucous TA with shape and distribution close to TA of SSc-patients (14). Abnormalities of endoglin gene has also been reported in SSc-patients (15,42). Finally, TA has been described in patients with cancer treated by an anti-endoglin monoclonal antibody (43). At present, it is not known whether anti-endoglin antibodies are present in SSc-patients. These data suggest that dysregulation of endoglin expression or function may be related to the development of the vasculopathy in SSc-patients.

We found no association between the number of TA and VEGF. VEGF, a powerful pro-angiogenic factor, can increase the vascular permeability, stimulates the migration and proliferation of endothelial cells and induces tube formation (13). Several studies have shown an overexpression of VEGF in the skin and serum of SSc-patients, particularly in the earliest stages of the disease and with the late NVC pattern, but none of them has studied the relationship with TA (13,44,45). The absence of difference found in our study can be partially explained by the existence of an antiangiogenic splicing variant, named VEGF 165b, detected by the kits usually used to measure

VEGF (46,47). An interesting strategy for studying VEGF could be to analyze the VEGF-165b/VEGF ratio to better differentiate the pro or anti-angiogenic effect of these factors.

Altogether these results suggest that (i) TA is associated with the most severe manifestations of vasculopathy in SSc, which could explain why we found that male gender was independently associated with TA, as the vascular disease is more severe in men (48); (ii) Endoglin could be implicated in the manifestations of the vasculopathy in SSc.

Strengths and limits

To our knowledge, we are the first to precisely describe the total number and distribution of TA on the whole body in SSc-patients, contrary to other studies, which made a semi-quantitative collection of TA using a non-validate TA score, either on the whole body or on certain parts (5,6,8).

The main limit of our study is the cross-sectional design, which does not allow establishment of a temporal relationship between the presence of TA and the subsequent development of vascular complications. Further prospective studies are necessary to determine if the number of TA may serve as an early clinical biomarker for the development of severe vascular disease, including PAH.

CONCLUSION

In conclusion, our study is the first to have quantitatively counted TA on the whole body. We showed that TA were predominantly located on the face, hands and the upper part of the trunk and that there was a good correlation between the number of TA on the face and/or hands and the total number of TA.

We showed an association between the number of TA and several vasculopathy features including PAH, pulmonary embolism, microvascular abnormalities of the skin and renal involvement. Interestingly, we also found an association with sEndoglin, suggesting the involvement of this angiogenic factor in the development of TA. Finally, we showed that the number of TA on the hands and/or face could be use in clinical practice to identify patients that require further investigations in search of PAH.

Thus, the number of TA may reflect the vasculopathy of SSc and could represent a clinical biomarker for vascular disease, particularly for PAH, one of the most severe vascular complications of the disease.

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REFERENCES

1. Johnson SR. New ACR EULAR guidelines for systemic sclerosis classification. Curr Rheumatol Rep. mai 2015;17(5):32.
2. Asano Y, Sato S. Vasculopathy in scleroderma. Semin Immunopathol. 8 juill 2015;37(5):489‑500.
3. Mould TL, Roberts PJ, others. Pathogenesis of telangiectasia in scleroderma. Asian Pac J Allergy Immunol. 2000;18(4):195–200.
4. Robert-Thomson, Mould, Walker JG, Smith MD, Ahern MJ. Clinical utility of telangiectasia of hands in scleroderma and other rheumatic disorders. Asian Pac J Allergy Immunol; 2002.
5. Shah AA, Wigley FM, Hummers LK. Telangiectases in Scleroderma: A Potential Clinical Marker of Pulmonary Arterial Hypertension. J Rheumatol. 1 janv 2010;37(1):98‑104.
6. Hurabielle C, Avouac J, Lepri G, de Risi T, Kahan A, Allanore Y. Skin telangiectasia identify a subset of Systemic Sclerosis patients with severe vascular disease. Arthritis Care Res. 1 oct 2015;n/a-n/a.
7. Zhang S, Xu D, Li M, Hou Y, Wang Q, Tian Z, et al. Telangiectasia as a potential clinical marker of microvascular lesions in systemic sclerosis patients from EUSTAR data in China. Clin Exp Rheumatol. août 2015;33(4 Suppl 91):S106-110.
8. Yalcinkaya Y, Pehlivan O, Omma A, Alpay N, Erer B, Kamali S, et al. The relationship between nailfold capillaroscopic assessment and telangiectasia score with severity of peripheral vascular involvement in systemic sclerosis. Clin Exp Rheumatol. août 2015;33(4 Suppl 91):S92-97.
9. Braverman IM, Ken-Yen A. Ultrastructure and three-dimensional reconstruction of several macular and papular telangiectases. J Invest Dermatol. déc 1983;81(6):489‑97.
10. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis. juill 2014;73(7):1340‑9.
11. Hachulla E, Launay D. Diagnosis and classification of systemic sclerosis. Clin Rev Allergy Immunol. avr 2011;40(2):78‑83.
12. Matura LA, Mcdonough A, Carroll DL. Health-related Quality of Life and Psychological States in Patients With Pulmonary Arterial Hypertension. J Cardiovasc Nurs. 1 janv 2014;29(2):178‑84.
13. Liakouli V, Cipriani P, Marrelli A, Alvaro S, Ruscitti P, Giacomelli R. Angiogenic cytokines and growth factors in systemic sclerosis. Autoimmun Rev. août 2011;10(10):590‑4.
14. Lafyatis R. Transforming growth factor β—at the centre of systemic sclerosis. Nat Rev Rheumatol. déc 2014;10(12):706‑19.
15. Dharmaplltn AK, Smith MD, Ahern MJ, Simpson A, Li C, Kumar S, et al. The TGF~ Receptor Endoglin in Systemic Sclerosis. Asian Pac J Allergy Immunol. 2001;19(4):275.
16. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. févr 1988;15(2):202‑5.
17. Valentini G, Rossa AD, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, et

al. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. Ann Rheum Dis. 1 juin 2001;60(6):592‑8.
18. Medsger TA, Bombardieri S, Czirjak L, Scorza R, Della Rossa A, Bencivelli W. Assessment of disease severity and prognosis. Clin Exp Rheumatol. 2003;21(3 Suppl 29):S42-46.
19. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. févr 1980;23(2):137‑45.
20. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 1 juill 2002;166(1):111‑7.
21. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 1 juin 2008;177(11):1248‑54.
22. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 1 janv 2016;37(1):67‑119.
23. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. avr 2017;2(1):11‑8.
24. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol. janv 2000;27(1):155‑60.
25. R Development Core Team. R. A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2008.
26. Halachmi S, Gabari O, Cohen S, Koren R, Amitai DB, Lapidoth M. Telangiectasis in CREST syndrome and systemic sclerosis: correlation of clinical and pathological features with response to pulsed dye laser treatment. Lasers Med Sci. 14 mars 2013;29(1):137‑40.
27. Aird WC. Endothelial Cell Heterogeneity. Cold Spring Harb Perspect Med. 1 janv 2012;2(1):a006429‑a006429.
28. Ennis H, Herrick AL, Cassidy C, Griffiths CEM, Richards HL. A pilot study of body image dissatisfaction and the psychological impact of systemic sclerosis-related telangiectases. Clin Exp Rheumatol. avr 2013;31(2 Suppl 76):12‑7.
29. Fichel F, Baudot N, Gaitz J-P, Trad S, Barbe C, Francès C, et al. Systemic Sclerosis with Normal or Nonspecific Nailfold Capillaroscopy. Dermatology. 2014;228(4):360‑7.
30. Pizzorni C, Giampetruzzi AR, Mondino C, Facchiano A, Abeni D, Paolino S, et al. Nailfold capillaroscopic parameters and skin telangiectasia patterns in patients with systemic sclerosis. Microvasc Res. mai 2017;111:20‑4.
31. Schoenfeld SR, Choi HK, Sayre EC, Aviña-Zubieta JA. Risk of Pulmonary Embolism and Deep Venous Thrombosis in Systemic Sclerosis: A General Population-Based Study: Venous Thromboembolism in SSc. Arthritis Care Res. févr 2016;68(2):246‑53.

32. Chung W-S, Lin C-L, Sung F-C, Hsu W-H, Yang W-T, Lu C-C, et al. Systemic sclerosis increases the risks of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study. Rheumatology. 1 sept 2014;53(9):1639‑45.
33. Zöller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. The Lancet. 2012;379(9812):244–249.
34. Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ. Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study. BMC Med. 2011;9(1):1.
35. Cerinic MM, Valentini G, Sorano GG, D'Angelo S, Cuomo G, Fenu L, et al. Blood coagulation, fibrinolysis, and markers of endothelial dysfunction in systemic sclerosis. Semin Arthritis Rheum. avr 2003;32(5):285‑95.
36. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360(18):1851–1861.
37. Momin A, Melikian N, Wheatcroft SB, Grieve D, John LC, El Gamel A, et al. The association between saphenous vein endothelial function, systemic inflammation, and statin therapy in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg. août 2007;134(2):335‑41.
38. Fujimoto M, Hasegawa M, Hamaguchi Y, Komura K, Matsushita T, Yanaba K, et al. A Clue for Telangiectasis in Systemic Sclerosis: Elevated Serum Soluble Endoglin Levels in Patients with the Limited Cutaneous Form of the Disease. Dermatology. 2006;213(2):88‑92.
39. Rathouska J, Jezkova K, Nemeckova I, Nachtigal P. Soluble endoglin, hypercholesterolemia and endothelial dysfunction. Atherosclerosis. déc 2015;243(2):383‑8.
40. Wipff J, Avouac J, Borderie D, Zerkak D, Lemarechal H, Kahan A, et al. Disturbed angiogenesis in systemic sclerosis: high levels of soluble endoglin. Rheumatology. juill 2008;47(7):972‑5.
41. Gregory AL, Xu G, Sotov V, Letarte M. Review: The enigmatic role of endoglin in the placenta. Placenta. févr 2014;35:S93‑9.
42. Wipff J, Kahan A, Hachulla E, Sibilia J, Cabane J, Meyer O, et al. Association between an endoglin gene polymorphism and systemic sclerosis-related pulmonary arterial hypertension. Rheumatology. 13 oct 2006;46(4):622‑5.
43. Rosen LS, Hurwitz HI, Wong MK, Goldman J, Mendelson DS, Figg WD, et al. A Phase I First-in-Human Study of TRC105 (Anti-Endoglin Antibody) in Patients with Advanced Cancer. Clin Cancer Res. 1 sept 2012;18(17):4820‑9.
44. Riccieri V, Stefanantoni K, Vasile M, Macrì V, Sciarra I, Iannace N, et al. Abnormal plasma levels of different angiogenic molecules are associated with different clinical manifestations in patients with systemic sclerosis. Clin Exp Rheumatol. avr 2011;29(2 Suppl 65):S46-52.
45. Distler O, del Rosso A, Giacomelli R, Cipriani P, Conforti ML, Guiducci S, et al. Angiogenic and angiostatic factors in systemic sclerosis: increased levels of vascular endothelial growth factor are a feature of the earliest disease stages and are associated with the absence of fingertip ulcers. Arthritis Res Ther. 2002;4(6):R11.
46. Harper SJ, Bates DO. VEGF-A splicing: the key to anti-angiogenic therapeutics? Nat Rev Cancer. 2008;8(11):880–887.
47. Manetti M, Guiducci S, Romano E, Ceccarelli C, Bellando-Randone S, Conforti ML, et al. Overexpression of VEGF165b, an Inhibitory Splice Variant of Vascular

Endothelial Growth Factor, Leads to Insufficient Angiogenesis in Patients With Systemic Sclerosis. Circ Res. 22 juill 2011;109(3):e14‑26.
48. Panopoulos ST, Bournia V-K, Sfikakis PP. Is vasculopathy associated with systemic sclerosis more severe in men? J Rheumatol. 2013;40(1):46–51.

ANNEXES

Les télangiectasies dans la sclérodermie systémique

Les télangiectasies (TA) sont des macules érythémateuses cutanées ou muqueuses due à la dilatation de capillaires ou de veinules. Morphologiquement, les TA peuvent être divisées en deux groupes : maculaires (pouvant être linéaires, stellaires, ramifiées, punctiformes…) ou papulaires (49) (Figure 4).

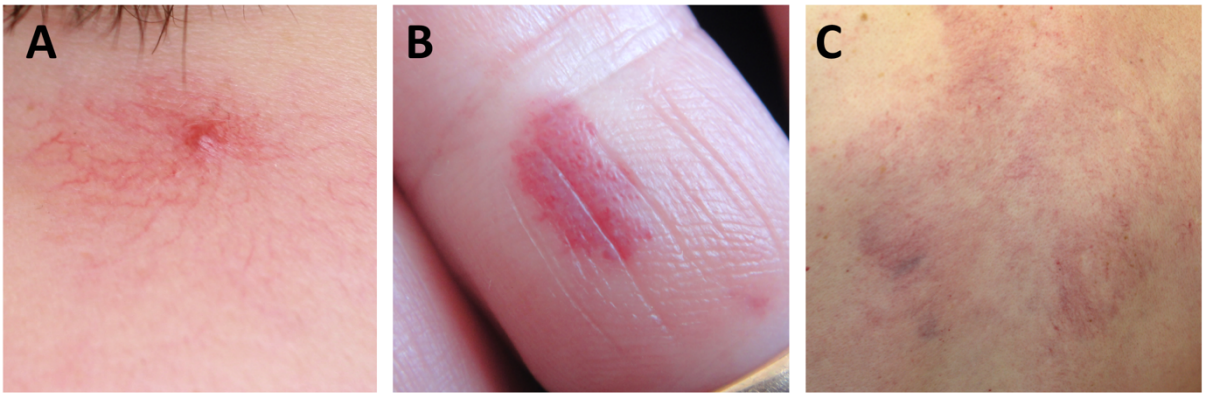

Figure 4 : Différents types morphologiques de télangiectasies : (A) une forme papulaire, et deux formes maculaires avec (B) une télangiectasie punctiforme et (C) des télangiectasies linéaires.

Les TA maculaires, les plus fréquentes, ont de multiples étiologies. Elles peuvent être causées par des agressions physiques ou chimiques (photodermatose, radiothérapie, dermocorticoïdes), être l'expression d'une pathologie plus générale, ou bien être primitives. Parmi les causes secondaires, on retrouve des pathologies dermatologiques (la rosacée, la dermite séborrhéique, la poïkilodermie de Civatte, la poïkilodermie atrophique vasculaire), ou systémiques (la mastocytose, la maladie de Rendu-Osler, certaines granulomatoses, les connectivites) (49).

La sclérodermie systémique (ScS) est la connectivite où les TA sont les plus fréquentes (Figure 5) (4). Sur le plan histologique, elles correspondent à la dilatation des veinules post-capillaires du plexus veineux horizontal supérieur situé dans le derme papillaire et réticulaire supérieur. La paroi vasculaire est épaissie due à la fois à une prolifération endothéliale et une prolifération des péricytes et des cellules musculaires lisses. Il n'est habituellement pas décrit d'infiltrat inflammatoire périvasculaire (9,26,50,51).

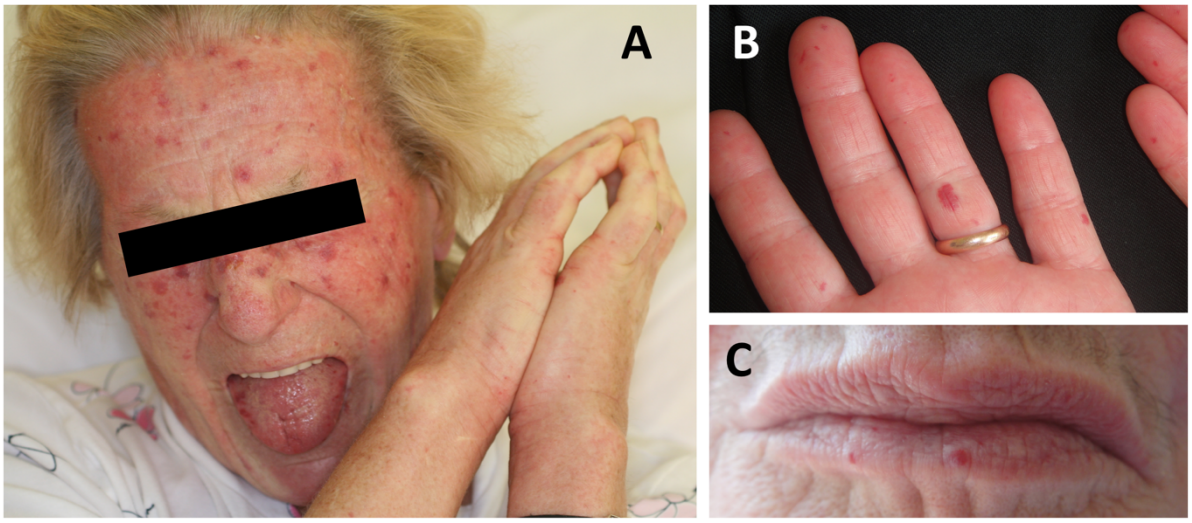

Figure 5 : Les télangiectasies au cours de la sclérodermie systémique : localisation sur le visage et la langue (A), sur les mains (B) et sur les lèvres (C).

Les mécanismes biologiques précis responsables du développement des TA sont actuellement peu connus. Elles pourraient être l'expression cutanéomuqueuse d'une tentative d'augmentation de la perfusion sanguine des tissus hypoxiques par la stimulation de l'angiogenèse. Il s'agit d'un mécanisme permettant la formation de néo-vaisseaux à partir d'un réseau vasculaire préexistant, finement régulé par des facteurs pro et anti-angiogéniques tels que les voies du Vascular Endothelial Growth Factor (VEGF) et du Transforming Growth Factor β (TGF-β). La voie du VEGF est composée

de cinq types de VEGF (VEGF-A, VEGF-B, VEGF-C, VEGF-D, Placental growth factor ou PIGF) capables de lier 3 récepteurs différents (VEGFR1, 2 et 3). VEGF-A est le plus étudié. En se liant au VEGFR2, il promeut l'angiogenèse, alors que VEGFR1 et sa forme soluble (sVEGFR1) diminuent l'angiogenèse en séquestrant VEGF-A (52). Par ailleurs, VEGF165b, un isoforme de VEGF-A est un inhibiteur compétitif de l'angiogenèse en se fixant à VEGFR2 sans induire la transduction du signal intracytoplasmique (46). Le TGF-β a un rôle antiangiogénique en interagissant avec le récepteur hétérodimérique ALK5/TGFR2 et un rôle proangiogénique en se liant au récepteur ALK1/TGFR2. L'endogline, une protéine membranaire, facilite la liaison du TGF-β avec ALK-1/TGFR2. Son absence, diminue l'angiogenèse, stimule les processus pro-fibrosants et augmente la production d'endotheline-1 (ET-1), un puissant vasoconstricteur et inducteur de l'angiogenèse (14,53). Enfin, le TGF-β, intervient également dans l'augmentation de la production du VEGF-A et du VEGF165b (54). Chez les patients sclérodermiques, le VEGF et l'endogline soluble semblent être des marqueurs de la vasculopathie (13,15,44). Leur rôle dans le développement des TA reste à définir.

Les TA ont surtout un retentissement esthétique chez les patients (28). Lorsqu'elles se situent sur les muqueuses digestives, il existe cependant un risque d'hémorragie (3).

Il n'existe pas de traitement général des TA à ce jour. Le traitement est uniquement local, par pulse dye laser. De par l'épaississement de leur paroi vasculaire, les TA des patients sclérodermiques sont plus résistantes au traitement que les TA d'autres pathologies, et nécessites donc un plus grand nombre de séances (55).

Complément des références bibliographiques pour les annexes

49. Gupta R, Gautam RK, Bhardwaj M, Chauhan A. A clinical approach to diagnose patients with localized telangiectasia. Int J Dermatol. 2015;54(8):e294–e301.
50. Walker JG, Stirling J, Beroukas D, Dharmapatni K, Haynes DR, Smith MD, et al. Histopathological and ultrastructural features of dermal telangiectasias in systemic sclerosis: Pathology (Phila). juin 2005;37(3):220‑5.
51. Kazandjian S, Bruneval P, Fiessinger JN, Camilleri JP, Housset E. Active proliferation of telangiectases in skin of patients with progressive systemic sclerosis (PSS). Arch Dermatol Res. 1986;279(1):8‑11.
52. Matsumoto K, Ema M. Roles of VEGF-A signalling in development, regeneration, and tumours. J Biochem (Tokyo). 1 juill 2014;156(1):1‑10.
53. Castañares C, Redondo-Horcajo M, Magán-Marchal N, Dijke P ten, Lamas S, Rodríguez-Pascual F. Signaling by ALK5 mediates TGF-β-induced ET-1 expression in endothelial cells: a role for migration and proliferation. J Cell Sci. 1 avr 2007;120(7):1256‑66.
54. Nowak DG, Woolard J, Amin EM, Konopatskaya O, Saleem MA, Churchill AJ, et al. Expression of pro- and anti-angiogenic isoforms of VEGF is differentially regulated by splicing and growth factors. J Cell Sci. 15 oct 2008;121(20):3487‑95.
55. Burillo-Martinez S, Prieto-Barrios M, Velasco-Tamariz V, Tous-Romero F, López-Gómez S, Maroñas-Jimenez L. Case series of pulsed dye laser treatment of telangiectasia in 23 patients with systemic sclerosis. Int J Dermatol [Internet]. mars 2017 [cité 11 avr 2017]; Disponible sur: http://doi.wiley.com/10.1111/ijd.13595

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Date de Soutenance : 30 juin 2017 à 16h
Titre de la Thèse : Les télangiectasies au cours de la sclérodermie systémique : distribution et associations clinico-biologiques

Thèse - Médecine - Lille 2017
Cadre de classement : Médecine interne
DES + spécialité : Médecine interne
Mots-clés : sclérodermie systémique, télangiectasies, vasculopathie, hypertension artérielle pulmonaire, thrombose veineuse, endogline soluble

Résumé :

Contexte : Les télangiectasies (TA), fréquentes au cours de la sclérodermie systémique (ScS), sont un critère de classification de la maladie, et pourraient être un marqueur clinique de la sévérité de la vasculopathie, notamment de l'hypertension artérielle pulmonaire (HTAP). Notre étude visait à décrire la distribution des TA sur l'ensemble du corps, puis à déterminer leur association avec les caractéristiques clinico-biologiques des patients ScS pour enfin préciser leur utilité dans l'identification des patients atteint d'HTAP.

Méthode : Les patients étaient inclus dans cette étude transversale s'ils validaient les critères ACR/EULAR 2013 de la ScS**.** Ceux ayant bénéficié d'un traitement par laser n'étaient pas inclus. Nous avons recueilli quantitativement les TA sur l'ensemble du corps, délimité en 16 zones corporelles. Les associations entre le nombre de TA et les caractéristiques clinico-biologiques étaient étudiées par régression linéaire en analyse univariée, ajustée puis multivariée.

Résultats : Nous avons inclus 106 patients de notre Centre de Référence National dont 12 ayant une HTAP. La répartition des TA était : 37,1% sur le visage, 33,2% sur les membres supérieurs dont 26,4% sur les mains, 28,1% sur le tronc dont 17,0% sur sa partie supérieure et 1,5% sur les membres inférieurs. En analyse multivariée, le nombre de TA était indépendamment associé à l'HTAP (p=0,038), l'embolie pulmonaire (p=0,012), l'endogline soluble (p=0,034), la diminution du débit de filtration glomérulaire (p=0,038) et le sexe masculin (p=0,033). Concernant l'identification de l'HTAP, les aires sous les courbes ROC du nombre de TA sur l'ensemble du corps, sur les mains, et à la fois sur le visage et les mains étaient respectivement de 0,77(0,57-0,89), 0,77(0,57-0,88) et 0,81(0,57-0,91).

Conclusion : Chez les patients atteint de ScS, les TA sont principalement localisées sur le visage, les mains et la partie supérieure du tronc. Elles sont le témoin de la vasculopathie présente dans la maladie notamment pulmonaire et peuvent être utilisées comme marqueur clinique afin d'aider à l'identification des patients atteint d'HTAP.

Composition du Jury :
Président : Pr Pierre-Yves Hatron
Assesseurs : Pr Eric Hachulla, Pr Sylvain Dubucquoi, Dr Jonathan Giovannelli, Pr David Launay (directeur de thèse)