Telangiectasia as a potential clinical marker of microvascular lesions in systemic sclerosis patients from EUSTAR data in China

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ABSTRACT

Objective. *To investigate the prevalence and clinical relevance of telangiectasia in Chinese patients with systemic sclerosis (SSc).*

Methods. *Data from 230 SSc EUSTAR patients from Peking Union Medical College Hospital (2009–2011) that fulfilled the 1980 American College of Rheumatology SSc classification criteria were prospectively collected. Demographic, clinical, and laboratory data were calculated between groups with and without telangiectasia, and a six-minute walk test, pulmonary function test (PFT), transthoracic echocardiography (TTE), right heart catheterisation (RHC) and modified Rodnan skin score (mRSS) were performed.*

Results. *96 patients (41.7%) were diagnosed with telangiectasia. There were no significant differences between patients with and without telangiectasia based on gender, age at onset, Raynaud's phenomenon (RP) duration, or SSc classification. Disease duration both from RP onset of patients and from first non-RP manifestation of patients with telangiectasia was significantly longer than patients without ($p<0.05$). RP (97.9% vs. 90.3%), finger/toe sclerosis (96.9% vs. 88.1%), facial sclerosis (68.8% vs. 53.7%), digital ulcers (DUs; 40.6% vs. 23.1%), digital pitting (49.0% vs. 33.8%), joint contracture (20.8% vs. 10.4%) and erythrocyte sedimentation rate elevation (26.7% vs. 14.8%) were significantly greater in telangiectasia patients ($p<0.05$). There were no differences in autoantibody development between patients with and without telangiectasia ($p>0.05$). PFT showed that forced vital capacity (77.0±17.26 vs. 83.05±16.53, $p=0.005$) and diffusion capacity for CO of the lung (58.9±19.4 vs. 65.7±19.7, $p=0.030$) were lower, while forced expiratory volume ratio (87.02±7.8 vs. 84.33±7.1, $p=0.029$) was higher in SSc with telangiectasia. Pulmonary artery hypertension (PAH) prevalence (25.0% vs. 14.2%) was significantly greater in patients with telangiectasia.*

Conclusion. *Telangiectasia are common in Chinese SSc patients and usually associated with DUs, RP, and PAH. Telangiectasia could be a clinical marker of microvascular disease in SSc.*

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterised by excessive collagen deposition in skin and internal organs (heart, lungs, kidneys, and gastrointestinal tract) (1). Two major groups of SSc patients can be identified based on the distribution of skin changes (2). Patients are considered to have diffuse skin disease if skin changes are found proximal to the elbows and/or knees or on the trunk, excluding the face. The other patients are considered to have limited disease if skin changes occur distal to the elbows and/or knees and not on the trunk. Facial skin thickening can be present in the limited group. It is generally agreed that CREST syndrome is part of the limited subset. Telangiectasia with other four features, calcinosis, Raynaud's phenomenon, oesophageal dysfunction and sclerodactyly are composed CREST syndrome.

Telangiectasia is the erythema produced by the widening of blood vessels. It is common feature of microvascular changes in SSc. Other manifestations, including Raynaud's phenomena (RP), digital ulcers (DUs), pulmonary artery hypertension (PAH) and renal crisis are also microvascular lesions of SSc. Some study has also suggested that gastroesophageal reflux (GER) might susceptible to microvascular damage of SSc patients (3). The mechanism of telangiectasia development in SSc re-

mains unknown, although it is possible they result from abnormal circulation in affected tissues. Moreover, telangiectasia could be a potential clinical biomarker of systemic vascular lesions and abnormal vascular remodelling of SSc (4). However, there are no reports of epidemiological or other characteristics of telangiectasia in Chinese SSc patients.

It is well known that some microvascular lesions, including PAH and renal crisis, are the main causes of death in SSc patients. It is a remarkable problem for us to recognise early. Therefore, we aimed to prospectively investigate the prevalence and clinical features of SSc patients with telangiectasia in China.

Materials and methods

Patients

Data from 230 SSc patients were prospectively collected from the European League Against Rheumatism Scleroderma Trial and Research Group (EUSTAR) database of Peking Union Medical College Hospital (Beijing, China) from February 2009 to December 2011. All patients fulfilled the classification criteria for SSc proposed by the 1980 American College of Rheumatology (5). This study was approved by the medical ethics committee of Peking Union Medical College Hospital (Beijing, China) and ethics committee of EUSTAR (6, 7). Telangiectasia was clinically defined as macroscopically visible dilated capillaries or venules occurring in the skin. They are vascular lesions composed of vasodilated postcapillary venules without evidence of neovascularisation or inflammation (8, 9). Any clinically visible telangiectasia on the face, limbs, chest, or abdomen was recorded by at least two rheumatologists. Our data were recorded from the weekly clinic for scleroderma, which was conducted by a senior and a junior rheumatologist. The junior rheumatologist recorded the clinical symptoms and physical examination of each patient, which were then confirmed by the senior rheumatologist. According to the 1980 ACR SSc criteria, only the limited and diffused skin disease patients were enrolled, patients overloaded other CTD, such as systemic lupus erythematosus and rheumatoid arthritis were excluded. RP duration was defined as the mean duration from RP to non-RP manifestation onset. Datas of disease duration from RP onset and from first non-RP manifestation were collected as well. DUs were defined as denuded areas with defined borders and loss of epithelialisation, epidermis, and dermis. Joint contractures were recognised as the loss of joint motion or high resistance to passive stretch. In SSc, joint contractures can be due to fibrosis of the tissue supporting the muscles or joints, such as tendons and ligaments, or the muscles themselves. Myositis was defined as creatine kinase elevation and/or myogenic damage by electromyogram. Sclerodactyly means thickening of the skin of the digits of the hands and feet. Digital pitting was defined as pinhole-sized digital concave depressions with hyperkeratosis. Erythrocyte sedimentation rate (ESR) elevation was defined as ESR >30 mm/h. PAH was defined as pulmonary artery systolic pressure (PASP) ≥40 mmHg at rest as estimated by transthoracic echocardiography (TTE) (10) and/or mean PASP ≥25 mmHg with a wedge pressure <15 mmHg via right-heart catheterisation (RHC). Interstitial lung disease (ILD) was evaluated by chest computerised tomography.

Demographics, symptoms, and signs were collected from all patients. Laboratory findings including ESR, C-reactive protein, immunoglobulin, complements, and autoantibody measurements were calculated, as well. Complements included C3, C4 and CH50. Autoantibody included antinuclear antibody (ANA), anti-dsDNA antibody, anti-Sm antibody, anti-U1RNP antibody, anti-SSA antibody, anti-SSB antibody, anti-Scl-70 antibody and anti-centromere antibody (ACA). Relative examinations included a six minute walk test, pulmonary function test, TTE and modified Rodnan skin score (mRSS).

Statistical analysis

SPSS software version 17.0 was used for data analysis. Continuous variables (mean±SD) were determined using the non-parametric test, and categorical variables were determined using the Pearson chi-square test. A $p<0.05$ was considered statistically significant.

Results

Demographic data

96 patients (41.7%) had telangiectasia out of 230 patients analysed. The majority of patients were women (89.6%) out of 230 patients analysed. The mean age of SSc onset was 42.2±14.6 years. Disease duration from RP onset of patients with telangiectasia was significant longer than patients without (98.5±78.7ms *vs*. 72.3±85.8ms $p=0.020$). Disease duration from first non-RP manifestation of patients with telangiectasia was also significant longer than patients without (86.5±72.8ms *vs*. 60.6±85.5ms $p=0.018$). Among the 230 patients, 57.9% had limited skin disease and 42.1% had diffused skin disease. There was no significant difference between patients with and without telangiectasia based on gender, age of onset, RP duration or SSc classification.

Clinical manifestations

The clinical characteristics between SSc with and without telangiectasia were compared. The presence of RP ($p=0.041$), finger/toe sclerosis ($p=0.017$), face sclerosis ($p=0.022$), DUs ($p=0.004$), joint contracture ($p=0.029$), and digital pitting ($p=0.021$) occurred significantly more frequently in patients with telangiectasia. However, no significant differences were found with other clinical features (Table I).

Laboratory findings

The prevalence of ESR elevation (26.7% *vs*. 14.8%) and C3 decrease (7.5% *vs*. 1.0%) was significantly greater in patients with telangiectasia than in those without. There were no significant differences in autoantibodies between patients with and without telangiectasia ($p>0.05$). Pulmonary function test showed that forced vital capacity (FVC%; 76.5±17.3 *vs*. 83.4±16.7, $p=0.005$) and diffusion capacity for carbon monoxide of the lung (DLCO%; 58.9±19.4 *vs*. 65.7±19.7, $p=0.030$) were lower, while forced expiratory volume ratio (87.02±7.8 *vs*. 84.33±7.1, $p=0.029$) was higher in SSc patients with telangiectasia than

Table I. Comparison of demographic data and clinical manifestations between SSc patients with and without telangiectasia.

	Without Telangiectasia (n=134)	With Telangiectasia (n=96)	*p*-value
Age at onset (years)	42.2 ± 16.5	42.2 ± 12.8	1.000
Gender (F/M)	117/17	88/8	0.296
RP duration (months)	11.7 ± 62.9	11.9 ± 63.7	0.974
Disease duration from RP onset (months)	72.3 ± 85.8	98.5 ± 78.7	***0.020***
Disease duration from first non-RP manifestation (months)	60.6 ± 85.5	86.5 ± 72.8	***0.018***
SSc subsets (d/l)	53/74	37/50	0.908
Skin involvement			
Digital ulcers	31 (23.1%)	39 (40.6%)	***0.004***
Finger/toe sclerosis	118 (88.1%)	93 (96.9%)	***0.017***
Face skin sclerosis	72 (53.7%)	66 (68.8%)	***0.022***
Digital pitting	45 (33.8%)	47 (49.0%)	***0.021***
RP	121 (90.3%)	94 (97.9%)	***0.031***
Joint and muscle			
Arthritis	52 (38.8%)	47 (49.0%)	0.125
Joint contracture	14 (10.4%)	20 (20.8%)	***0.029***
Myositis	41 (26.8%)	43 (36.7%)	0.080
Respiratory system			
ILD	95 (70.9%)	71 (74.0%)	0.609
PAH	19 (14.2%)	24 (25%)	***0.038***
Pericardial effusion	15 (11.1%)	7 (7.7%)	0.345
Diastolic dysfunction	10 (7.8%)	12 (12.8%)	0.117
Decrease LVEF	0 (0)	2 (2%)	0.107
GI system			
Acid reflex	53 (40.0%)	44 (45.8%)	0.341
Diarrhoea	23 (15.0%)	26 (22.2%)	0.129
Dysphagia	50 (32.7%)	41 (35.0%)	0.684

F: Female; M: Male; d: diffuse skin disease; l: limited skin disease; RP: Raynaud's phenomenon; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; LVEF: left ventricular ejection factor; GI: gastrointestinal.

Table II. Comparison of laboratory findings between SSc patients with and without telangiectasia.

	Without Telangiectasia (n=134)	With Telangiectasia (n=96)	*p*-value
ESR elevation (>30mm/h)	18/122 (14.8%)	23/86 (26.7%)	***0.032***
IgG elevation (>17g/l)	38/121 (31.4%)	35/82 (42.7%)	0.100
Decrease CH50 (<25U/ml)	5/99 (5.1%)	1/71 (1.4%)	0.219
Decrease C4 (<0.12g/l)	6/97 (6.2%)	4/65 (6.2%)	0.502
Decrease C3 (<0.6g/l)	1/102 (1.0%)	5/67 (7.5%)	***0.033***
Anti-centromere (+)	19 (14.1%)	12 (12.5%)	0.713
Anti-SCL-70 (+)	61 (45.5%)	38 (39.6%)	0.370
6MWT	488.0 ± 106.2	467.9 ± 99.9	0.201
mRSS	7.37 ± 7.45	8.73 ± 7.91	0.186
Pulmonary function test			
FVC (%)	83.4 ± 16.7	76.5 ± 17.3	***0.005***
FEV1/FVC	84.33 ± 7.09	87.02 ± 7.82	***0.02***9
TLC (L)	4.45 ± 1.09	4.19 ± 1.09	0.112
DLCO (%)	65.7 ± 19.7	58.9 ± 19.4	***0.030***
FVC% / DLCO%	1.34 ± 0.38	1.43 ± 0.48	0.208

ESR: erythrocyte sedimentation rate; 6MWT: 6-minute walk test; mRSS: modified Rodnan skin score; PFT: pulmonary function test; FVC: forced vital capacity; FEV1: forced expiratory volume for the first minute; TLC: Total lung capacity; DLCO: diffusion capacity for carbon monoxide of the lung.

in those without. Moreover, there was significantly more PAH in patients with telangiectasia compared to those without (p=0.038) and no significant differences in CT scan for ILD, mRSS and the six-minute walk test (Table II). Among 230 patients, 21 patients underwent RHC, of which 17 was found PAH.

Discussion

Telangiectasia is a common feature of microvascular changes in SSc. To our knowledge, this is the first study investigating the characteristics of Chinese SSc patients with telangiectasia. Previously, two Japanese studies of 33 and 211 SSc patients reported the prevalence of telangiectasia in SSc patients to be 39.4% and 56%, respectively (11, 12). Similar to the Japanese study, we found that telangiectasia was prevalent in 41.7% of Chinese patients with SSc. In addition, we also found no significant differences between patients with and without telangiectasia based on gender, age at onset, or RP duration, as with the Japanese study (12). We got the results that patients with telangiectasia had longer disease duration both from RP onset and from first non-RP manifestation. It suggested that SSc patients with longer disease duration might have more chances to get telangiectasia.

CREST syndrome is a subtype of limited scleroderma. Although most previous studies found an increased telangiectasia frequency in the limited SSc subset, several studies showed that telangiectasias are equally frequent in both forms of the disease (13, 14). Our results showed no significant difference in different SSc subtypes. In addition, while telangiectasia can be found in both subtypes of SSc, patients with telangiectasia were more likely to have sclerodactyly, although their mRSS was not higher.

It is now recognised that microvascular dysfunction plays a fundamental role in the pathogenesis and associated tissue injury in SSc. Microvascular lesions represent pathogenic manifestations in SSc, including telangiectasia, RP, DUs, renal crisis and PAH (15). Based on our results, significant correlations were found between telangiectasia with RP,

DUs, and PAH. Previous studies have concluded that clinically visible matlike telangtiectasia is important diagnostic factor in patients with SSc, just as RP is (16). Telangtiectasia is one of the seven additive items apply of the 2013 new classification criteria for SSc, which has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee (17). Since DUs are often difficult to treat and can substantially reduce the patients' quality-of-life, their prevention and early treatment is critical. According to our results, telangtiectasia could be a potential barometer for DUs. Thus, it is important for SSc patients with telangtiectasia to prevent and/or treat digital ischaemia, keep warm, and take a vasodilator to prevent DU formation.

PAH is another pathogenic manifestation that results from dysfunction of the microvasculature in SSc. Since PAH can be fatal in SSc patients, more clinical biomarkers are needed to identify and predict PAH. Shah *et al*. (2010) reported a strong association between the increased prevalence of telangiectasia and elevated right ventricular systolic pressure and RHC-confirmed PAH. They concluded that cutaneous telangiectasia could be a clinical biomarker of pulmonary vascular disease (18). Peter *et al*. (2007) reported the possible association of telangiectasias of the hands with isolated pulmonary hypertension (19). In addition, we also found a correlation between the telangiectasia and PAH which suggested that telangiectasia was a potential marker of PAH. Altough there were no differences of PAH prevalence between patients with and without telangiectasia through RCH evaluation, we thought it was too few patients undergoing RCH to get reasonable results of the correlation between PAH and telangiectasia. Moreover, because PAH detection requires special equipment resulting in higher medical costs, identifying key PAH risk factors and early screening is important for SSc patients' diagnoses and therapy. Telangiectasia of the skin is often highly visible, requiring no special equipment; therefore, they can be used as a simple screen for PAH. The FVC% was utilised as the index of restrictive ventilatory dysfunction and was commonly used to evaluate the severity of (ILD (20). Our study showed FVC% of patients with telangiectasia was significantly lower than those without. The previous Japanese study showed the incidence of a decreased FVC% was greater in patients with telangiectasia than in those without, although not significantly (12). They also found that the DLCO% was significantly lower in those with telangiectasia, which was similar to our results. There was no difference between the two groups with ILD in both our results and the Japanese. Unfortunately, whether a correlation exists between telangiectasia and pulmonary function, as well as ILD, remains controversial.

Telangiectasia also directly influences patients' quality-of-life, as patients with facial telangiectasia worry about their visual appearance (21). Furthermore, telangiectasia treatment includes additional medications, laser treatments, and surgery, which can increase their level of stress (22, 23). The gold standard for the treatment of telangiectasia and superficial blood vessels is pulsed dye laser, which is based on the principle of selective photothermolysis (24, 25). Shlomit *et al*. (2013). found that all telangiectatic lesions responded to treatment, but that CREST telangiectasia required approximately twice as many treatments as control lesions (26). In summary, this is the first report on the prevalence of telangiectasia in Chinese patients with SSc. We found that telangiectasias are usually associated with DUs, RP, and PAH, and may be a clinical marker of microvascular disease in SSc.

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