Clinical characteristics of systemic sclerosis patients with digital ulcers in China

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ABSTRACT

Objective. *To investigate the clinical characteristics of SSc patients with DUs in China.*

Methods. *The data of 267 consecutive SSc patients based on the EUSTAR DATABASE from Peking Union Medical College Hospital from February 2009 to March 2012 were prospectively collected. The patients with DUs were compared to those without DUs.*

Results. *Seventy-nine patients (29.6%) had DUs out of 267 SSc patients analysed. There were significant differences between patients with and without DU based on sex (female/male: 65/14 vs. 174/14), age of onset of SSc (32.3±11.7 vs. 40.4±12.6 y), age of onset of Raynaud's phenomenon (31.8±12.3 vs. 38.7±12.2) ($p<0.05$). In addition, there was a higher rate of diffuse SSc, gastrointestinal involvement, (especially esophageal involvement), and pericardial effusion, higher mRodnan score, and more anti-scl70 antibody positivity in patients with DU ($p<0.05$). A multivariate analysis identified anti-Scl70 antibody positivity, gastrointestinal involvement and a younger age at disease onset as three risk factors for developing DUs in SSc patients.*

Conclusion. *The occurrence of DUs in Chinese SSc patients is frequent. It is possible that SSc patients with DUs were influenced by the disease earlier in life, which should be detected early for effective intervention.*

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease of unknown etiology. The dysfunction of microvasculature is a key feature of SSc, and the outcome usually depends on the extent and severity of vascular lesions. Microvascular lesions underlie several manifestations of SSc, including Raynaud's phenomenon (RP), digital ulcers (DUs), pulmonary arterial hypertension (PAH), and renal crisis. In contrast to PAH and renal crisis, which lead to increased mortality in SSc patients, DUs can cause local pain and functional impairment. In addition, chronic ulcers can become infected (1), resulting in gangrene, osteomyelitis, and subsequent amputation (2). DUs are often difficult to treat and are slow to cure, which markedly reduces the quality-of-life and increases the social economic burden of SSc patients. A European League Against Rheumatism scleroderma trial and research group (EUSTAR) multicenter study of 3656 SSc patients estimated the prevalence of DU in SSc patients to be 36.7%, and a German study of 1690 SSc patients estimated the prevalence of active DU in SSc patients at the time of entering the registry to be 24.1% (3, 4). However, there are currently no reported data on DUs in Chinese patients with SSc. Therefore, the aim of this study was to investigate the prevalence and clinical characteristics of SSc patients with DU in China.

Patients and methods

Patients

A prospective study analysing the medical charts from 267 consecutive SSc patients registered in the EUSTAR database of Peking Union Medical College Hospital (PUMCH) from February 2009 to March 2012 was conducted. All patients fulfilled the American College of Rheumatology (ACR) classification criteria from 1980 for SSc. DU was defined as a loss of both the epidermis and dermis in the fingers. Patients with active or completely healed DUs were compared to patients without DUs. Gastrointestinal involvement is defined as the presentation of one of the following symptoms: esophageal symptoms (dysphagia, reflux), stomach symptoms (early satiety, vomiting), or intestinal symptoms (diarrhoea, constipation, bloating) or existing gastrointestinal lesion confirmed by

radiology or endoscopy. PAH is defined as a mean pulmonary arterial pressure of >25mmHg at rest or >30mmHg during exercise together with a pulmonary capillary wedge pressure of <15mmHg through right heart catheterisation or a pulmonary artery systolic pressure >40mmHg at rest based on an echocardiogram test. Pulmonary fibrosis is defined as ground glass opacification or fibrosis on high-resolution computed tomography (CT). The reduced left ventricular ejection fraction (LVEF) was defined as LVEF less than 50%. The elevation of erythrocyte sedimentation rate (ESR) was defined as more than 20 mm/h. The elevation of C reactive protein (CRP), IgG, IgM and IgA was defined as values greater than the normal ranges. The reduction of CH50, C3 and C4 was defined as values less than the normal value.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS, Chicago, IL) was used for data processing and analysis. Continuous variables (mean ± standard deviation) were determined using the non-parametric test, and categorical variables were determined using the Pearson chi-squared test. Clinical manifestations with *p*-values less than 0.05 in the univariable analyses were further investigated using binary logistic regression analysis. A *p*-value less than 0.05 was considered statistically significant.

Results

Demographic data

Two hundred and sixty-seven patients were enrolled. The age of onset of SSc was 38.0±12.9y (8.1~75.2y), female/male ratio was 239/28, duration of RP was 84±86.0mo (1~460mo), and disease subset (diffuse/limited) was 116/151, respectively.

Seventy-nine patients (29.6%) had active or completely healed DUs out of the 267 SSc patients analysed. Forty-three patients (16.1%) had active DUs at the time they were evaluated. The prevalence of DUs in diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) was 38.8% and 22.5%, respectively. The age of onset for patients with DU was 35.9±12.9 years (range: 8.1–62.3 years). Significant differences were found between patients with and without DUs based on sex (female/male: 65/14 *vs*. 174/14, respectively; p=0.016), age of onset of SSc (32.3±11.7 *vs*. 40.4±12.6 years, respectively; p<0.001), and age of onset of RP (31.8±12.3 *vs*. 38.7±12.2 years, respectively; p<0.001). There were no significant differences in the time of disease evolution from the occurrence of the first non-RP phenomenon in patients with DU and without DU (93.0±93.2 *vs*. 67.2 ±119.7 months, respectively; p=0.089).

Table I. Comparison of clinical manifestations and laboratory findings between SSc patients with and without DUs.

	SSc without DU (n=188)	SSc with DU (n=79)	*p*-value
SSc subset (dcSSc/lcSSc)	71/117	45/34	*0.005*
Raynaud's phenomenon	173 (92.0%)	78 (98.7%)	*0.045*
Articular involvement	98 (52.1%)	34 (43.0%)	0.183
Gastrointestinal	104 (55.3%)	57 (72.2%)	*0.013*
esophageal dysmotility	91 (48.4%)	50 (63.3%)	*0.032*
stomach involvement	36 (19.1%)	23 (29.1%)	0.078
intestinal involvement	46 (24.5%)	18 (22.8%)	0.875
Respiratory system involvements	125 (66.5%)	57 (72.2%)	0.391
pulmonary interstitial fibrosis	118 (62.8%)	54 (68.4%)	0.404
pulmonary arterial hypertension	35 (18.6%)	17 (21.5%)	0.613
Renal involvement			
renal crisis	3 (1.6%)	2 (2.5%)	0.634
proteinuria	5/157* (3.2%)	4/60* (6.7%)	0.265
haematuria	21/158* (13.3%)	11/61* (18.0%)	0.397
Heart involvement			
reduced LVEF	2/157* (1.3%)	0/58* (0%)	1.000
reduced diastolic dysfunction	24/156* (15.4%)	3/58* (5.2%)	0.062
pericardial effusion	15/156* (9.6%)	12/58* (20.7%)	*0.038*
Heart conduction block	2/101* (2.0%)	1/35* (2.9%)	1.000
Muscle weakness	60 (31.9%)	30 (38.0%)	0.395
mRodnan score	6.7 ± 6.7	10.8 ± 8.7	<0.001
ACA positivity	30/124* (24.2%)	5/46* (10.9%)	0.086
Anti-SCL70 antibody positivity	63/155* (40.6%)	44/69* (63.8%)	*0.001*
Anti-RNP antibody positivity	44/147* (29.9%)	13/58* (22.4%)	0.304
ESR elevation	60/169* (35.5%)	21/70* (30.0%)	0.455
CRP elevation	78/121* (64.5%)	31/49* (63.3%)	1.000
IgG elevation	62/169* (36.7%)	26/65* (40.0%)	0.654
IgA elevation	26/168* (15.5%)	9/65* (13.8%)	0.840
IgM elevation	16/168* (9.5%)	3/65* (4.6%)	0.291
CH50 reduction	1/144* (0.7%)	0/54* (0%)	1.000
C3 reduction	4/148* (2.7%)	2/54* (3.7%)	0.659
C4 reduction	16/147* (10.9%)	6/53* (11.3%)	1.000

*means positive case number/actual tested total case number.
dcSSc: diffuse SSc; lcSSc: limited SSc; LVEF: left ventricular ejection fraction.

Clinical manifestations and laboratory findings

There were significant differences between patients with and without DUs in the SSc subset and those with RP, gastrointestinal involvement, esophageal involvement, pericardial effusion, higher mRodnan score, and anti-scl70 antibody positivity (Table I). However, no significant differences were found in other clinical manifestations, such as PAH and other laboratory tests (p>0.05).

Clinical manifestation and laboratory findings of DU patients with dcSSc and lcSSc were also analysed. There were significant differences between dcSSc patients with and without DUs based on the age of onset of SSc (30.8±10.5 *vs*. 39.6±13.0 years, respectively; p<0.001), age of onset of RP (30.3±11.0 *vs*. 39.1±12.7 years, respectively; p<0.001), gastrointestinal involvement (80.0% *vs*. 47.7%, respectively; p=0.016), and anti-scl70 antibody positivity (30/37 *vs*. 29/60, respectively; p=0.001). There were also significant differences between lcSSc patients with

and without DUs based on the age of onset of SSc (34.4±13.1 *vs*. 40.9±12.4 years, respectively; p=0.009) and mRodnan score (5.8±4.2 *vs*. 3.9±3.1, respectively; p=0.018).

Treatment

Symptomatic therapy used to treat SSc patients with DU was as follows: Bosentan (2 cases: 2.5%), Beraprost (3 cases: 3.8%), Sildenafil (2 cases: 2.5%), calcium-channel blocker (22 cases: 27.8%), angiotensin converting enzyme inhibitors/angiotensin receptor antagonist (2 cases: 2.5%), and aspirin (38 cases: 48.1%).

Logistic regression analysis

A multivariate analysis identified anti-Scl70 antibody positivity, gastrointestinal involvement, and a younger age at the time of SSc onset as three risk factors for developing DUs in SSc patients (Table II).

A multivariate analysis was also performed for dcSSc and lcSSc patients. Anti-Scl70 antibody positivity, younger age at the time of SSc onset, and esophageal dysmotility were identified as three risk factors for developing DUs in dcSSc patients (Table III). However, no risk factor was identified in lcSSc patients.

Table II. Multivariate analysis of SSc patients with DUs.

	OR	95% confidence interval		*p*-value
Anti-Scl-70 antibody positivity	2.112	1.064	4.191	0.033
Age at onset of SSc	0.953	0.925	0.981	0.001
gastrointestinal involvement	2.249	1.109	4.560	0.013

OR: odds ratio.

Table III. Multivariate analysis of dcSSc patients with DUs.

	OR	95% confidence interval		*p*-value
Anti-Scl-70 antibody positivity	5.415	1.547	18.960	0.008
Age at onset of SSc	0.924	0.875	0.976	0.005
Esophageal dysmotility	4.310	1.236	15.027	0.022

OR: odds ratio.

Discussion

This is the first reported study to investigated the characteristics of Chinese SSc patients with DUs. DUs are frequent in Chinese SSc patients, and according to our database the prevalence is approximately 30%, which is similar to that reported in other countries (1, 3, 4). The patients in our study were relatively young, which was similar to the patients reported in the Deutsches Netzwerk für Systemische Sklerodermie (DNSS) study, where the mean age was 42.6 and 44.6 y for SSc patients with and without DUs, respectively (p=0.03). A younger age at onset of SSc is an independent risk factor of DU. In addition, we found that of the patients who had an onset of RP, the patients with DUs were younger than patients without DUs at the time of RP emergence. These findings suggest that SSc patients with DUs were influenced by the disease earlier in life.

Interestingly, although females have a higher risk for SSc than males and the prevalence of SSc in females is ten times higher than males (5), the prevalence of DUs in females with SSc was significantly lower than males with SSc. These results indicated that being male was the highest independent risk factor of DUs in SSc patients (4). Based on these results, close attention should be made for the emergence of DUs in younger male SSc patients with earlier onset of RP.

In agreement with previous reports (3, 5), our cluster anaylsis showed that the number of the lcSSc subset of patients was slightly higher than the number of the dcSSc subset in China. Moreover, our data and previous reports both showed that DUs were more frequent in dcSSc patients as well as SSc patients with anti-Scl70 antibody positivity and severe skin sclerosis (3, 4, 6-8). The latter conditions were more common in dcSSc patients. Therefore, we hypothesise that a variety of factors, such as vasculopathy and fibrosis, may all contribute to the pathogenesis of DU.

In agreement with studies by the DNSS and Canadian Scleroderma Research Group (CSRG), we found RP, esophageal dysmotility and anti-Scl70 antibody positivity were risk factors for DUs (4, 9). Our previous study showed that SSc-related gastroesophageal reflux is associated with microvascular damage (10), which could explain why DU is common in patients with eso-phageal dysmotility. Moreover, this study is the first to identify pericardial effusion as one risk factor for DUs. However, in dcSSc and lcSSc pericardial effusion had no correlation with DU. Until now, no reports have analysed the correlation between pericardial effusion and DU. We hypothesise that the pericardial effusion was be induced by microvascular damage; however, additional studies are needed to explore the mechanism. Furthermore, although vasculopathy is an indication of both PAH and DUs, it remains controversial whether PAH is a risk factor for DUs (4, 6, 8, 9). Our study found no correlation between PAH and DU. Therefore, it is possible that both PAH and DU are a result of vasculopathy with no causal relationship. Moreover, the number of patients in our study was low, and therefore a larger scale study should be conducted to investigate the relationship between PAH and DU.

SSc is characterised by fibrosis, and elevation of inflammatory indicators does not commonly occur (5). It has been reported that the serum level of IL-6 and soluble CD40 ligand is elevated in SSc patients with DU (11, 12), which suggests that inflammation and activation of T lymphocytes may play an important role in the pathogenesis of DU. Therefore, we questioned whether elevation of ESR, which is an indicator of inflammation, is associated with DU. Our study did not find any correlation between elevated ESR and DU.

The field of rheumatology continues to explore precise approach to study DUs and new tools for predicting DUs and outcome in SSc patients. Amanzi *et al*. showed an evidence-based DU subsetting according to their origin and main characteristics, which provided a standard platform and increased the credibility and repeatability in randomised controlled trials and therapeutic studies (13). Sebastiani *et al*. reported that the capillaroscopic skin ulcer risk index (CSURI) can predict the onset of new DUs by using nailfold videocapillaroscopy (NVC) in SSc patients, and thus NVC represents a novel tool that has the ability to predict the development of DUs in SSc patients (14). Kayser *et al*. found avascular scores higher than 1.5 at NVC was an independent predictor of death in SSc (15). Moreover, a current study showed alteration of microcirculation was a hallmark of very early SSc patients through a laser speckle contrast analysis, which showed us the important role of microangiopathy in the pathogenesis of SSc (16). However, to date, NVC has been relatively unexplored and little attention was paid to DUs in China.

In summary, the occurrence of DUs in SSc patients is frequent in China, therefore more attention should be given to it during our practice. Importantly, young males with diffuse SSc should be assessed and monitored closely for the development of DUs.

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