Natural History of Ischemic Digital Ulcers in Systemic Sclerosis: Single-Center Retrospective Longitudinal Study

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ABSTRACT. ***Objective.*** To describe the natural history of ischemic digital ulcers (DU) in systemic sclerosis (SSc).

Methods. This single-center, retrospective, longitudinal study identified patients by demographic data, SSc history and type, Rodnan score, tobacco use, presence of autoantibodies, ongoing treatment, and DU history.

Results. One hundred three patients were enrolled, 46 with DU history and 57 without; 2 with DU were excluded. The mean duration of followup from the first non-Raynaud SSc symptoms was 12.3 ± 6.3 years in patients with DU history and 12.1 ± 7.0 years in patients without. In 43% of cases, first DU occurred within 1 year following first non-Raynaud SSc symptoms, and within 5 years in 73% of cases. In a multivariate analysis, younger patients at occurrence of first non-Raynaud SSc symptoms (HR = 0.77 per each 5 years older, 95% CI 0.66–0.90) with higher Rodnan scores (HR = 1.21 per 5 points, 95% CI 1.05–1.47) experienced earlier DU occurrences, which were delayed by vasodilator therapy (HR = 0.17, 95% CI 0.09–0.32). Patients with shorter durations between first and second DU episodes, particularly with a second episode within 2 years of the first, experienced a higher yearly incidence of DU episodes (0.85 ± 0.57 and 0.48 ± 0.26, respectively, if less or more than 2 yrs; p = 0.04). Throughout the duration of followup, the incidence of finger amputation was 1.2% per patient-year in patients with DU history.

Conclusion. Patients who are young at first sign of SSc, with high Rodnan scores and without vasodilator therapy, are at high risk of developing DU. Development of DU typically occurred within 5 years of the first non-Raynaud clinical symptom of SSc in the majority of patients. (First Release Nov 1 2007; J Rheumatol 2007;34:2423–30)

Key Indexing Terms:
SYSTEMIC SCLEROSIS SCLERODERMA DIGITAL ULCER NATURAL HISTORY

Systemic sclerosis (SSc) is a chronic disease primarily resulting from vascular, autoimmune and proliferative disturbances. Classification is based on early presentation and progression of cutaneous involvement, and is specified as diffuse SSc, limited cutaneous SSc (formally known as CREST syndrome), or limited scleroderma (known as SSc sine scleroderma)[1–3]. Often, the very first manifestation of SSc is as Raynaud's phenomenon (RP), episodic attacks of vasoconstriction of the small arteries that are precipitated by cold or emotional stress and occur in over 90% of patients with SSc[4].

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In patients with SSc, the lumen of cutaneous and systemic peripheral arteries and arterioles is narrowed due to fibrosis of the intimal layer[5]. Such obliterative vasculopathy of the small vessels may lead to ischemic digital ulcers (DU) developing on the tips of the fingers[6]. The pathophysiology of DU in SSc is complex, involving both ischemic and mechanical phenomena.

Three principal types of DU exist, and may be distinguished as: (1) ulcers occurring at bony prominences, usually at metacarpophalangeal or interphalangeal joints of the fingers, promoted by microtraumatic events and by traction exerted on the sclerous skin when the fingers are flexed; (2) ulcerations occurring at the level of subcutaneous calcifications where mechanical and inflammatory phenomena are also involved; and (3) ischemic DU that occur most frequently on distal areas of fingers, involving pulp or sometimes lateral edges.

Mechanical and ischemic phenomena are frequently related, with mechanical ulcers often occurring in areas of skin with sclerodermic microangiopathy. Whatever the type, DU are frequent among patients with SSc, with 15%–25% having active DU[7] and 35%–50% having, or having experienced DU[8,9], although estimates vary[10]. DU are painful, slow to

heal, and can sometimes be complicated by secondary infections (superficial infection or osteitis). The pain caused by DU has a disabling effect on patients, particularly regarding grip, feeding, dressing, and hand hygiene[11]. Severe DU episodes sometimes necessitate hospitalization and require time away from the workplace[11].

Ours is the first study to describe the natural history of ischemic DU in SSc.

MATERIALS AND METHODS

From a French screening program for pulmonary arterial hypertension (PAH) that involved a nationwide cohort of 599 patients, we identified the 103 patients that our clinic included in the study. At inclusion, demographic data, SSc history and type, date of first occurrence of RP, date of first non-RP clinical symptom of SSc, and history of or current DU due to peripheral ischemia were documented for each patient. Additionally, Rodnan score, tobacco use, presence of anti-Scl-70 and anticentromere antibodies, ongoing treatment for RP, and the history and presence of DU were evaluated. Patients were classified as having limited or diffuse SSc according to Leroy, *et al*[2]. Patients with SSc were typically monitored at least twice a year, with detailed descriptions of their DU systematically reported. DU occurrences between SSc onset and inclusion in the PAH screening program were collected retrospectively using patient records.

Between July and September 2006, all patients were contacted in order to accurately reconstitute their DU history. Patients with only a single DU episode were contacted by telephone, and patients with several previous DU episodes were seen in consultation. All patients gave informed consent to inclusion in the study. DU histories were collected beginning with the first occurrence of DU to the last visit or contact, and the history of SSc was reconstituted beginning with patients' first non-RP clinical symptom of SSc. We did not take into account the natural history of ulcers that occurred above calcifications or above bone relief, which have more mechanical supports.

Since several DU may occur in a single episode, an episode was defined as being "All DU that developed within 2 months of each other, which remained unhealed at the time of development of the final DU in that episode." For each episode, data collected included the start date of the first DU, topography of all DU, time to complete healing of all DU in an episode, ongoing treatment at the time of first DU, treatment for DU, duration of hospitalization (if any), and administration of systemic antibiotics.

Infected DU were defined as those with local inflammation and chronic development, and confirmed whenever possible by bacterial analysis. In the absence of bacteriological evidence, the clinical judgment of the expert SSc physician was enrolled to confirm diagnosis of infection. Osteitis was defined as bone infection confirmed by surgical biopsy, with bacterial analysis or positive gallium scintigraphy. Surgical amputation, sympathectomy, arteriolysis, and arthrodesis were considered as major surgery. Details of the evolution of DU, as well the different management procedures for DU, were reviewed by the director of the center on the basis of the patient's records.

Statistical methods. Data were analyzed using SAS 8.2 software (SAS Institute, Cary, NC, USA). Categorical data were described using frequency and percentage; continuous data were summarized using mean and standard deviation, unless otherwise specified. The duration of disease was calculated from the first non-RP clinical symptom of SSc to the date of inclusion. Time from first non-RP clinical symptom of SSc to first occurrence of DU was estimated using the Kaplan-Meier method. Comparisons between strata were conducted by the log-rank test. For each patient, early incidence of DU episodes was determined by dividing the number of episodes by the duration of followup since their first DU. Multivariate analysis involved logistic regression for binary data and Cox models for time-to-event analysis.

RESULTS

Patient population. One hundred three consecutive patients with SSc were enrolled by our center in a nationwide French screening program for PAH. The history of DU since enrollment in this program could not be reconstituted from 2 patients with DU history: one died before data collection commenced and contact was lost with another one; therefore the analysis was performed using 101 patients. At inclusion into the PAH screening program, 44 patients had either a current DU or history of DU (DU subgroup), and 57 patients had no DU history (no DU subgroup). Of the 57 patients without DU history at enrollment in the PAH screening program, none had experienced DU afterwards and at least until the date of analysis.

Table 1 presents the demographic data and the main clinical and biological characteristics of all patients. The mean duration of SSc from the first non-RP clinical symptom of SSc was 12.3 ± 6.3 years [range 1.3–27.7; 95% confidence interval (CI) 10.4–14.2] in the DU subgroup and 12.1 ± 7.0 years (range 3.1–36.4; 95% CI 10.2-13.9) in the no DU subgroup. The mean followup duration at our center was 7.7 ± 3.5 years (median 7.2) and was similar between the 2 groups ($p = 0.96$). In the DU subgroup of patients, SSc onset occurred at a younger age, and diffuse SSc was also more frequent, in comparison with the cohort with no DU history. A DU history was observed in 15/22 (68%) patients with diffuse SSc, and in 29/79 (37%) patients with limited SSc. No difference was found in the prevalence of autoantibodies.

PAH occurred in 11 patients (11%) during the course of the disease and its prevalence was comparable between the subgroups (14% PAH in the DU subgroup and 9% PAH in the no DU subgroup; $p = 0.53$). At our center, usual therapy was calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, or other vasodilators in patients with severe or disabling RP. Out of the 44 patients in the DU subgroup, 21 were not taking vasodilators at time of the first DU, but thereafter, all received vasodilator therapy.

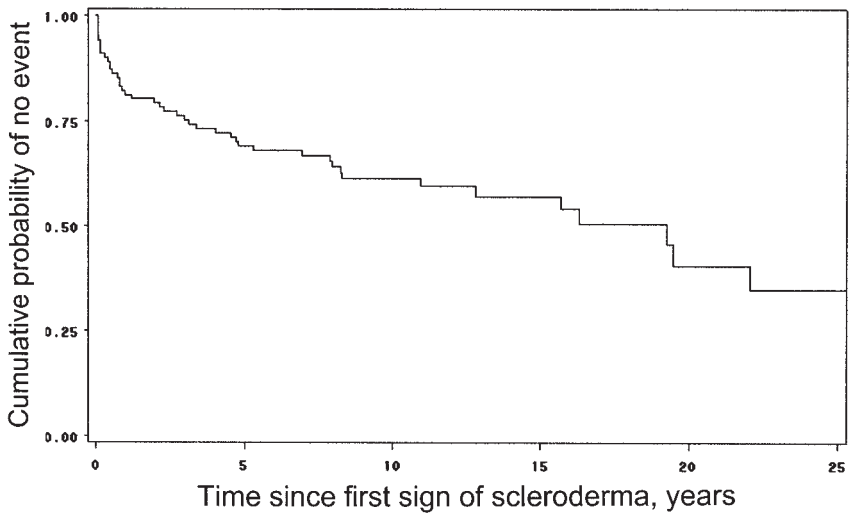
In the subgroup of patients without DU history, 6 patients had not taken vasodilators during the observation phase (odds ratio 0.13; 95% CI 0.05–0.36). In this group, one patient developed digital gangrene related to an antineutrophil cytoplasmic antibody-associated vasculitis with kidney involvement, a rare SSc complication not directly related to the classical scleroderma microangiopathy. Vasodilators were most frequently prescribed in patients with diffuse SSc ($p = 0.0005$), who were also younger at first non-RP clinical SSc symptom ($p = 0.001$). From 74 patients receiving vasodilators, 49 were treated with calcium channel blockers, 10 with ACE inhibitors, and 15 with other vasodilators.

Time to occurrence of the first digital ulcer. The development of DU was often relatively early in SSc disease course. The mean duration between the first non-RP SSc symptom and the occurrence of a first DU was estimated using the Kaplan-Meier method to be 13.5 ± 1.0 years (n = 101, mean ± SE). Twenty-five patients (25%) experienced DU within 3.1 years (95% CI 0.9–7.9; Figure 1). Cox modeling (multivariate

Table 1. Patient demographics and clinical characteristics.

	DU History	No DU History	p
Patients, n	44	57	
Women, n (%)	35 (80)	52 (91)	0.14
Age at first SSc symptom, yrs (mean ± SD)	42 ± 12 (38–45)	48 ± 11 (45–51)	0.01
Mean duration of SSc, yrs (mean ± SD)	12.3 ± 6.3 (10.4–14.2)	12.1 ± 7.0 (10.2–13.9)	0.86
Age at occurrence of first DU, yrs (mean ± SD)	46.3 ± 13.0 (42.3–50.2)	NA	
Duration between first non-Raynaud's symptom and first DU, yrs (median, 95% CI; Kaplan-Meier estimate)	2.2 (0.8–4.5)	NA	
Caucasians, n (%)	42 (95)	57 (100)	0.19
Smoking status, n (%)			
Nonsmokers	34 (77)	41 (72)	
Former smokers	8 (18)	8 (14)	0.26
Smokers	2 (5)	8 (14)	
Limited SSc/diffuse SSc, n (%)	29 (66)/15 (34)	50 (88)/7 (12)	< 0.0001
Rodnan score (mean ± SD)	11 ± 10 (8–14)	7 ± 6 (6–9)	0.02
Anticentromere antibodies, n (%)	22 (50)	36 (63)	0.18
Anti-Scl-70 antibodies, n (%)	12 (27)	12 (21)	0.47
PAH, n (%)	6 (14)	5 (9)	0.53

Data in parentheses are 2-sided 95% confidence intervals. DU: digital ulcers; SSc: systemic sclerosis; PAH: pulmonary arterial hypertension.



Time, yrs	0	2.5	5	7.5	10	12.5	15	17.5	20	22.5	25
No. at risk	101	101	97	85	75	65	58	53	51	50	48
Events	0	23	8	2	4	2	1	1	2	1	1
Censored*	0	4	12	10	10	7	5	2	1	2	—

Figure 1. Kaplan-Meier estimate of time to first digital ulcer after first sign of SSc in total population (n = 101). *Censored data: no episode between first sign of scleroderma and last visit.

analysis) demonstrated a correlation between younger age (hazard ratio 0.77 per each 5 years older, 95% CI 0.66–0.90) and higher Rodnan scores (HR 1.21 per 5 points, 95% CI 1.05–1.47) with earlier incidences of first DU. In a further Cox model, treatment with calcium channel blockers, ACE inhibitors, or vasodilators appeared to significantly delay the development of the first DU (HR 0.17, 95% CI 0.09–0.32, representing a relative risk reduction of DU history by 5.88),

along with Rodnan score (HR 1.21 per 5 points, 95% CI 1.05–1.40), whereas the influence of patient's age was no longer apparent.

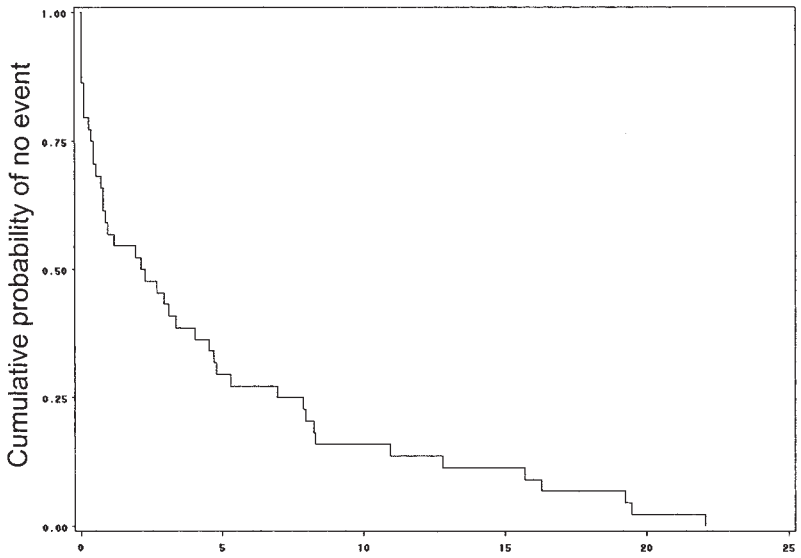
In the 44 patients with a history of DU, the median time between RP and the first ischemic DU was 6.0 years (95% CI 4.1–11.7, Kaplan-Meier estimate) and the median time between the first non-RP symptoms of SSc and the first ischemic DU was 2.2 years (95% CI 0.8–4.5, Kaplan-Meier estimate). In 19 patients with DU history (43%), the first DU occurred within 1 year of the first clinical sign of SSc, and within 5 years in 32 patients (73%) (Figure 2).

DU episodes after the first DU. The natural course of DU was described using data from the subgroup with DU history (n = 44). The median duration of followup after the first DU episode was 7.26 years. In total, 338 patient-years were analyzed, during which time 141 episodes involving 240 DU occurred. Episodes of DU were often recurrent, with 66% of patients having more than one episode and 50% having more than 2, despite the use in all cases of calcium channel blockers or other vasodilators. The yearly incidence of DU was 0.5 ± 0.5 episodes per patient per year (median 0.4). Five patients (11%) had more than one episode per year.

During the observational period, the mean duration between 2 episodes within the same patient was 3.3 ± 4.2 years (median 2.2), with 22 patients (50%) experiencing at least 2 episodes separated by less than 1 year (Figure 3). Ten out of 44 patients (23%) experienced a second episode within a year of the first, and 14 (32%) experienced a second episode within 2 years of the first. The estimated median time was 3.7 years (95% CI 2.8–7.5). In patients with at least 2 episodes, the mean yearly incidence of DU was greatest in patients with a shorter duration between the first 2 DU episodes (Table 2).

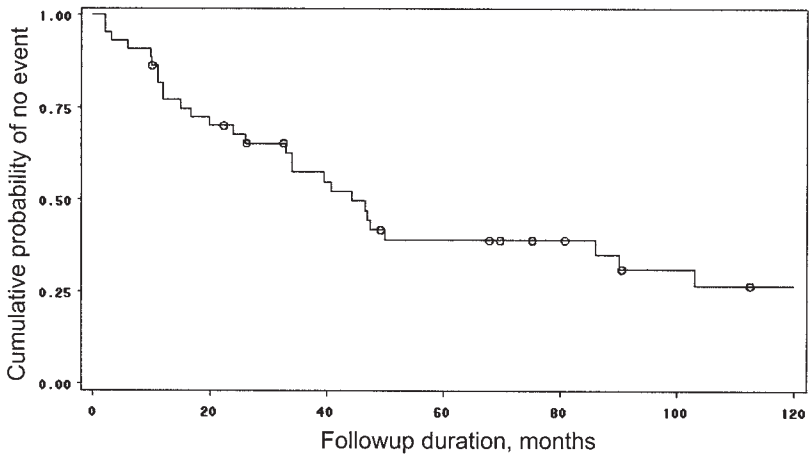
Clinical course of DU. The mean number of DU per patient per year was 0.83 ± 0.86 (range 0.05–3.65, median 0.50). During the followup period, the number of DU per patient reached 34 in one patient and > 5 in 8 patients (18%). DU were predominantly located on the palmar faces of fingers (94%) and seldom on the lateral edges (6%). DU were also mainly located on the distal phalanx (76%) and equally distributed between both hands (48.3% on left, 51.7% on right hands). DU occurred most frequently on the first 3 fingers (I: 19.66%, II: 32.5%, III: 32.5%), consistent with microtrauma being a contributory factor in their development. Ulcers were frequently multifocal in the same episode (39% of episodes, Table 3) and occasionally bilateral (16% of episodes).

Evolution and treatment of DU episodes. In the patients with



Time, yrs	0	2	5	10	15	20
No. at risk	44	23	13	7	5	1
Events	21	10	6	2	4	1
Censored*	0	0	0	0	0	0

Figure 2. Kaplan-Meier estimate of time to first digital ulcer (DU) after the first sign of scleroderma excluding Raynaud's phenomenon in the DU subgroup (n = 44). *Censored data: patients without DU between first sign of scleroderma and last visit.



Time, mo	0	12	24	36	48	60	72
No. at risk	44	43	32	26	22	16	13
Events	0	10	4	4	6	1	0
Censored*	1	1	2	0	0	2	2

Figure 3. Kaplan-Meier estimate of time to occurrence of a new DU episode after a first episode (n = 44). *Censored data: no further episode between first episode and last visit.

Table 2. Mean yearly incidence of DU episodes and duration between first 2 DU episodes.

Duration between First 2 DU Episodes*	Patients, n	Yearly Incidence of DU (mean ± SD)	p
< 1 yr	10	0.96 ± 0.61	
≥ 1 yr	19	0.50 ± 0.28	0.048
< 2 yrs	14	0.85 ± 0.57	
≥ 2 yrs	15	0.48 ± 0.26	0.04

* In patients with at least 2 episodes of DU.

Table 3. Number of digital ulcers per DU episode (from a total of 141 episodes).

No. Ulcers per Episode	Episodes, n (%)
1	86 (60.99)
2	27 (19.15)
3	16 (11.35)
4	10 (7.09)
6	2 (1.42)

a history of DU, episodes of ischemic DU were frequently associated with complications (Table 4) and healing times of 105 ± 97 days (range 5 days–2 yrs). Throughout the duration of followup of these patients with DU history, the incidence of

Table 4. Complications of ischemic digital ulcers.

	Episodes of DU, n = 141		Patients, n = 44	
	n	%	n	%
Ischemia (cold and cyanotic finger)	52	37	30	68
Gangrene	11	8	8	18
Infection	25	18	16	36
Osteitis	7	5	4	9
Infection or osteitis	32	23	18	41
Self-amputation	17	12	14	32
Amputation	4	3	3	7

infection or osteitis was 9.5% per patient-year, with 16 patients (36%) having at least one infected DU and 4 (9%) having at least one case of osteitis. Thirty-two out of 141 episodes (23%) required antibiotics for 39.2 ± 43.2 days (median 21.0), 25 for DU infections and 7 for associated osteitis. Systemic antibiotic treatment was necessary in 20 patients (46%): one course for 15 patients (35%) and several courses for 5 patients (11%), with mean treatment duration of 66 ± 96 days (range 10–376).

Thirty patients (68%) had critical finger ischemia at least once. Nine episodes of DU out of 141 (6%) were treated with intravenous vasodilators and 38 with parenteral prostanoids (27%) for 10 ± 6 days. Nineteen patients (43%) received at

least one course of iloprost and 9 patients (20%) received more than one course. The total duration of prostanoid treatment per patient reached 19 ± 22 days, corresponding to a total of 367 days of hospitalization. Twelve DU episodes out of 141 required opioid analgesia, 10 episodes for at least 3 months.

Amputation limited to one phalanx was necessary in 3 patients (7%), and one patient had 2 surgical amputations. Throughout the duration of followup, the incidence of finger amputation was 1.2% per patient-year in patients with DU history. One female patient had a sympathectomy at both wrists, within 1 year. Hospitalization due to DU severity was required in 47 out of 141 cases (33%), with mean duration of hospitalization being 8.6 ± 5.8 days per episode, and reaching 27 days for one episode. Twenty-five patients (57%) were hospitalized at least once for the management of their DU.

The severe effect of ischemic DU on the patient was also severe for the community. The total duration of hospitalization for DU treatment was 483 days, with some patients hospitalized several times. Throughout the duration of followup of the patients with DU history, the number of days of hospitalization was 1.43 days per patient-year. This represented a cost for the national health insurance system (Caisse d'Assurance Maladie) of €494,109 (483 x €1,023) or €1,462 per patient-year. To this amount, the cost of iloprost must be added (€27,158; 367 days x €74), corresponding to €80 per patient-year. The real cost is, indeed, notably higher since the associated, indirect costs of absence from work, analgesics and antibiotics taken, and the cost of ulcer care (consumables and nurse procedures) should also be considered. Moreover, it is difficult to estimate the *pretium doloris* for this pathology, which is occasionally extremely painful and a frequent cause of disability.

DISCUSSION

Ours is the first study to describe the natural history of ischemic DU in SSc. We have identified 103 patients with SSc, of whom 44 had a history of DU. The mean duration of followup since the first non-RP symptom of SSc was more than 12 years in all patients. In patients with at least one DU, the median duration of followup after the first episode of DU was 7.26 years, and overall, 338 patient-years were analyzed. Within this period, 141 episodes involving 240 DU were compiled and analyzed. In patients with at least one DU, the median duration of followup after the first episode of DU was 7.26 years. In addition, we have observed that patients who are young at the time of the first clinical presentation with SSc, with high Rodnan scores, and not in receipt of vasodilator therapy, have a higher risk of developing DU.

Our study estimates the prevalence of ischemic DU in SSc patients at 43%, consistent with an Italian study, which estimated the incidence in 1,012 patients during 5.1 years to be 48%[12]. In our study, DU were more frequently associated with diffuse SSc compared with limited SSc, with 68% of patients with diffuse SSc and 32% of patients with limited SSc having a DU history. This is consistent with observations from both the Italian and a French Canadian study[12,13]. Episodes of DU frequently involved several ulcers (39%), which were often bilateral (16%). The distribution of DU was roughly equal between both hands, with ulcers most frequently located on the palmar face of the first 3 fingers, consistent with a contribution of micro-trauma to their development.

DU typically occurred early in the course of SSc, and in 43% of patients, ischemic DU were observed within 1 year of the first non-RP SSc disease symptom. From the population of SSc patients that developed a DU, ulceration occurred in 73% of these patients within the first 5 years, an observation similar to that of a retrospective study in which 48% of patients with SSc developed a DU within 5.1 years after their first non-RP SSc symptom[14]. In another study, the median time between onset of RP and development of DU was 4.3 years[15]. We found no correlation between PAH and DU history, but it will require further studies to determine if ischemic DU history reflects a more severe vascular disease with higher risk of other vascular complications like renal crisis or PAH.

In patients who experienced multiple episodes of DU, the durations between episodes were relatively short. Patients with ulcers that recurred within 2 years of the first DU episode were more prone to future ulcerations than other patients, and may therefore constitute a subgroup at higher risk of recurrent ulceration. Patients with a more severe history of digital ischemia may therefore require more aggressive therapeutic intervention.

Our observations suggest that the absence of vasodilator therapy may have increased the risk of a first DU. While our study cannot assess the preventive role of vasodilators, it suggests that patients with SSc may derive benefit from vasodilator therapy initiated immediately following SSc diagnosis. This observation may be particularly relevant for young patients with a high Rodnan score. Treatment using nifedipine, prostaglandin E1, prostacyclin, and iloprost may deliver positive effects for patients with DU, although improvements are not always statistically significant[16–23]. In SSc patients with a history of DU, treatment using bosentan has been observed to prevent the occurrence of new DU[24,25].

In terms of the burden of DU on patients with SSc, this study has estimated the duration of hospitalization for DU treatment to be 1.4 days per patient-year. For patients with DU, the mean incidence of infection or osteitis was 9.5% per patient-year, and 1.2% per patient-year for finger amputations. These observations concur with findings from Prof. J.R. Seibold (University of Michigan), who reported a 1% annual incidence of amputation in SSc patients (Seibold, personal communication). Whilst our study did not evaluate pain, disability, or the need for analgesia, the effect of DU on these quality-of-life indicators has been investigated[11].

In our study, the clinical characteristics of patients were not dissimilar to those of patients from other centers included in

the PAH screening program. Additionally, the mean duration of disease was consistent with that observed in the French Canadian cohort[13]. However, the incidence rate of DU in the French Canadian patients with SSc was lower than in our study, and we hypothesize that this may be due to differences in climate and geography between these 2 regions. Given this, we are confident that these results can be extrapolated to all patients with SSc in France. However, in contrast to a recent British study, our findings suggest that tobacco use does not influence the likelihood of DU occurrences, although this may be due to a comparatively smaller sample size[14].

One limitation of our study is that the PAH screening program excluded patients with severe cardiac disease and severe pulmonary function abnormalities (defined as forced vital capacity or total lung capacity < 60%). Patients with severe pulmonary fibrosis more frequently have a diffuse form with a higher risk of DU. This could influence the real prevalence of DU in patients with SSc. Nevertheless, only 5 patients were excluded from the screening program at our center due to severe pulmonary fibrosis. Moreover, no difference was found between the patients of the DU subgroup and the patients of the no DU subgroup regarding FEV1 or forced vital capacity or total lung capacity. We cannot deny that these results may not be representative of all patients with SSc, and this prevalence of DU in patients with SSc may represent an underestimate of the total prevalence, but the true prevalence is certainly not very different from the prevalence we described. Moreover, 2 patients with DU history were excluded from our study because one died before the beginning of the study and the other was unable to be contacted, causing a possible selection bias. So the real burden of DU in this SSc population is probably underestimated.

Another potential limitation was the exclusion of DU without ischemic origin, such as ulcers resulting from mechanical events or ulcers over subcutaneous calcifications, as are most frequently found in patients with diffuse and limited SSc, respectively. However, the underlying causes of DU can be multifactorial, due to ischemia and sclerodactyly, dry skin, calcinosis, or local trauma. Superficial microulcerations, with diameters less than 1 mm and covered by hyperkeratosic lesions, were also excluded, as their natural history could not be accurately retrospectively determined. Patients presenting with this type of microulceration were usually those with recurrent DU.

One further limitation is that since our study determined the natural history of ischemic DU using data from medical files, there may have been some unintentional omissions. Records of DU were compiled using descriptive coding letters recorded at each visit. However, if minor episodes had been forgotten by patients between visits, these data will not have been included in the analysis, and this study may therefore underestimate the number and prevalence of ischemic DU.

Ours is the first study to describe the natural history of ischemic DU in SSc. In a multivariate analysis, we showed that younger age at onset of SSc and a higher Rodnan score increases the risk of developing a DU. Patients with SSc who are receiving vasodilator therapy have a lower risk of developing DU (reduction of the risk of a DU by 5.88). In patients with a history of DU, the occurrence of first DU was generally early in SSc disease course (occurrence within the first 5 yrs after the first sign of SSc in almost 75%), and was often contemporary with the first non-RP SSc disease symptoms. Patients that experience recurrent DU within 2 years of their first episode may constitute a subgroup of patients at higher risk of future recurrences, and may benefit from treatment other than classical vasodilators.

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