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The Challenge of Very Early Systemic Sclerosis: A Combination of Mild and Early Disease?

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ABSTRACT. ***Objective.*** To address the hypothesis that very early patients with systemic sclerosis (SSc) are a heterogeneous group with mild or early disease, we analyzed the extent of heterogeneity in clinical, epidemiological, and immunological characteristics of these patients.

Methods. We performed an analysis of very early SSc patients from the Zurich cohort, who fulfilled neither the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism nor the 1980 ACR classification criteria, but had a clinical expert diagnosis of SSc with Raynaud phenomenon (RP) and additional features of SSc (puffy fingers, SSc-specific antibodies, SSc pattern on nailfold capillaroscopy, or any organ involvement characteristic for SSc). Disease duration was defined from first RP symptom.

Results. One hundred and two patients fulfilled the inclusion criteria and were analyzed. Their clinical presentation was heterogeneous with the large majority presenting with RP, antinuclear antibodies, and nailfold capillaroscopy changes, but with varying presentations of other features such as SSc-specific antibodies and early signs of organ involvement. While 54.1% (52/96) of patients had a disease duration of < 5 years, as many as 29.1% (28/96) of patients had a disease duration of > 10 years, indicating long-standing mild disease. Patients with very early, potentially progressive disease did not differ from patients with long-standing mild disease in terms of their clinical features at first presentation.

Conclusion. This study showed that patients with very early SSc are a mixture with mild or early disease. This needs to be considered in clinical practice for risk stratification and for the study design of patients considered as early SSc.

Key Indexing Terms: autoimmune diseases, disease duration, systemic sclerosis

Systemic sclerosis (SSc) is a rare, chronic connective tissue disease with clinically heterogeneous manifestations. It has a high morbidity and mortality, which highlights the importance of detecting it at an early stage, where therapeutic interventions can prevent progression of organ damage[1,2]. However, the very early detection of SSc can be challenging. Although the new 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria have a higher sensitivity than the 1980 ACR classification criteria, there are still patients who do not fulfill the 2013 ACR/EULAR classification criteria but show early signs of SSc[3]. Analysis of this very early group of SSc patients is of particular interest and high importance for disease management because very early intervention has been shown to profoundly improve disease course and outcome in a variety of different inflammatory rheumatic diseases[4,5].

Very early SSc can be characterized by the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria, which includes a varying combination of Raynaud phenomenon (RP), puffy fingers, abnormal nailfold capillaroscopy (NFC) and antinuclear antibodies (ANA)/SSc-specific autoantibodies[6,7,8,9]. While these VEDOSS patients might represent early stages of SSc progressing into definite clinically established SSc, they also could represent a very mild form of SSc that will not progress to definite SSc. We currently lack validated criteria to differentiate very early, potentially progressive SSc patients from very mild, nonprogressive SSc patients. This is a major limitation for clinical practice, as very mild patients need a very different follow-up, risk stratification, and treatment strategy than potentially progressive

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patients. Very mild, stable patients should also not be recruited for clinical trials looking at early therapeutic interventions in VEDOSS patients. Thus, the question—whether patients who can be classified as VEDOSS are a mixed group of mild, stable SSc patients and early, progressive SSc patients—greatly affects both clinical practice and clinical trial design.

To address the hypothesis that VEDOSS patients are a heterogeneous group of mild and early patients, we analyzed the extent of heterogeneity in clinical, epidemiological, and immunological characteristics of very early SSc patients from the Zurich cohort.

MATERIALS AND METHODS

Clinical characteristics of the very early SSc patients from the Zurich cohort were analyzed in this study. They were consecutively recruited from the outpatient clinic and fulfilled neither the 2013 ACR/EULAR nor the 1980 ACR classification criteria for SSc, but had shown in addition to RP clinical features of SSc (puffy fingers, SSc-specific antibodies, SSc pattern on NFC or any organ involvement)[10,11,12]. Patients with primary RP (RP without any of the manifestations above) were excluded. All patients underwent the standard assessments for very early SSc as defined previously[7,13]. This included assessment by the detection of pulmonary arterial hypertension in SSc (DETECT) score, and patients with an increased score were sent for right heart catheterization[14]. Demographic and disease characteristics of the patients enrolled between January 2009 and June 2018 were analyzed cross-sectionally. All patients signed an informed consent for enrollment into the Zurich database. The study has been approved by the Cantonal Ethics Committee of Zurich and has been done according to the Declaration of Helsinki.

Disease duration was calculated as the difference between the baseline visit date and the date of the first RP symptom reported by the patient[15,16]. For further analysis, the cohort was divided into 2 subgroups using a cutoff value of < 5 and ≥ 5 years' disease duration. Frequency comparisons were made using chi-square test and Fisher exact test for categorical variables, and Mann-Whitney *U* test for continuous variables. Further, a binary logistic regression was conducted to analyze the association of disease duration and certain clinical features (puffy fingers, digital ulcers, joint contractures, and tendon friction rubs). Data were expressed as frequencies and percentages for categorical variables or as means ± SD and medians ± IQR for continuous variables.

RESULTS

A total of 102 patients met the inclusion and exclusion criteria and were available for analysis in this study. The patients' demographic and disease characteristics are shown in Table 1. Our data show that several variables were frequently present and thus similar among the very early SSc patients. Altogether 95/99 (96.0%) had ANA, 102/102 (100%) had RP, and NFC was abnormal in 61/79 (77.2%) patients. On the other hand, there was a remarkable heterogeneity in other clinical variables including autoantibodies (anticentromere antibodies 47.5%, anti-RNA polymerase III 5.2%, anti-Scl70 1.0%), puffy fingers (19.0%), telangiectasia (15.3%), gastrointestinal esophageal involvement (28.3%), joint synovitis (12.7%), and interstitial lung disease (5.2%; Table 1). None of the patients showed an increased DETECT score, and therefore, none were sent for right heart catheterization.

If all patients were early progressive patients, then disease duration must have been short, excluding patients with long-standing mild disease. In fact, median disease duration was 4.1 years (IQR 1.6–11.5; Table 1). While around 54% (52/96) of the patients had a disease duration of < 5 years, there was a considerable number of patients with long-standing disease

Table 1. Description of the study cohort at baseline (total N=102)

	N = 102
Age, yrs	53 (43–64)
Male	10 (9.8)
Female	92 (90.2)
RP	102/102 (100)
RP disease duration, yrs	4.1 (1.6–11.5)
Puffy fingers (ever)	19/100 (19.0)
Digital ulcers (ever)	2/79 (2.0)
mRSS	0 (0–0)
Musculoskeletal	
Joint synovitis	13/102 (12.7)
Tendon friction rubs	1/102 (1.0)
Cardiopulmonary	
Dyspnea (NYHA)	
Stage I	74/88 (84.1)
Stage II	11/88 (12.5)
Stage III	0/88
Stage IV	0/88
Lung fibrosis on chest HRCT	4/77 (5.2)
FVC < 80%	7/93 (7.5)
DLCO < 70%	7/93 (7.5)
PAH by RHC	0/0
Gastrointestinal	
Esophageal symptoms	28/99 (28.3)
Renal crisis	0/99
Laboratory markers	
ANA	95/99 (96.0)
ACA	47/99 (47.5)
Anti-Scl70	1/99 (1.0)
Anti-U1RNP	1/95 (3.2)
Anti-RNA polymerase III	5/96 (5.2)
CK elevation	12/99 (12.1)
Proteinuria	3/98 (3.1)
ESR > 25 mm/h	5/99 (5.0)
CRP elevation	6/97 (6.2)
Immunosuppressive treatment†	2/102 (2.0)
Abnormal NFC	61/79 (77.2)
Telangiectasia	13/85 (15.3)

For categorical variables, the absolute and relative frequencies are expressed as n/total valid cases (%). Continuous variables are expressed as median (IQR). † Immunosuppressive treatment is defined as prednisone ≥ 10 mg/day or any treatment with disease-modifying antirheumatic drugs or biologics. Variables are defined according to VEDOSS[7]. ACA: anticentromere antibodies; ANA: antinuclear antibodies; anti-Scl70 antibodies: anti-topoisomerase I antibodies; CK: creatine kinase; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; HRCT: high-resolution computed tomography; mRSS: modified Rodnan skin score; NFC: nailfold capillaroscopy; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; RHC: right heart catheterization; RP: Raynaud phenomenon; VEDOSS: Very Early Diagnosis of Systemic Sclerosis criteria.

(Figure 1). For example, as many as 29.2% (28/96) patients had a disease duration of > 10 years, virtually excluding them to be classified as early progressive SSc, but rather representing a long-standing, very mild form of SSc.

For clinical stratification, it is important to classify the patients as early, potentially progressive SSc upon their first presentation. Therefore, we wondered if patients with short and longer disease duration were presenting with different clinical characteristics. However, the clinical characteristics of early patients with < 5 and ≥ 5 years' disease duration showed no statistically significant differences in demographics and disease manifestations even though some clinical features had a higher percentage in patients with disease duration < 5 years such as puffy fingers (22.9% vs 14.0%), joint synovitis (15.4% vs 9.1%), telangiectasia (18.6% vs 13.5%), and DLCO < 70% (10.6% vs 5.0%). Proteinuria and increased C-reactive protein values were also found numerically more frequently in the group with shorter disease duration without reaching statistical significance (Table 2).

In addition, we wanted to assess whether certain clinical variables were independently associated with disease duration as a surrogate for early progressive disease. Clinical variables for logistic regression modeling were chosen based on recent publications and clinical rationale (puffy fingers, digital ulcers as markers of features occurring in patients with early SSc, and joint synovitis and tendon friction rubs being risk factors of disease progression in established SSc)[7,17,18,19]. However, there was no association of these risk factors and disease duration (data not shown).

DISCUSSION

Even though early detection of SSc is possible, it remains challenging to identify patients at high risk of progression into definite, clinically meaningful SSc. For such progressive patients, very early detection is of key importance for their overall disease outcome, as half of all incident organ manifestations occur simultaneously within 2 years from the first RP[5,20]. Previous studies also showed that digital ulcers and early internal organ involvement may be already present in VEDOSS patients, which was confirmed by our study[20].

However, our study provided an important finding: Patients fulfilling the criteria for very early SSc are a heterogeneous mixture with early disease potentially at risk of progression, and with long-standing, very mild SSc. The current classification of these patients should be reconsidered and needs to be divided into very mild/long-standing and very early, potentially progressive patients. This observation has important implications for the management of patients with very early disease. Patients with mild long-standing disease need different frequencies of follow-up and different considerations for therapeutic interventions than patients with very early disease at risk of progression. Our study also showed that these 2 subgroups of early/mild SSc cannot be easily differentiated based on clinical features on first presentation.

Our study has certain limitations. A limited number of variables was collected by the VEDOSS protocol. Items with > 50% of missing data were excluded from the analysis. The number of patients is rather small, although more than 100 patients were analyzed in our present study. We have taken long-standing disease duration as a measure of mild and stable disease, but it cannot be excluded that patients with very long-standing disease can have disease exacerbation and progression, although this seems rather unlikely from clinical experience. Vice versa, we also cannot exclude that those patients with short disease duration can have mild disease and will never progress. Most importantly, risk factors for progression can only be determined from longitudinal analysis. The VEDOSS study, the largest collection of patients with very mild SSc with a long-term longitudinal follow-up, will be able to address these questions.

In conclusion, our study showed that patients with very early SSc are in fact a mixture of patients with mild and early disease.

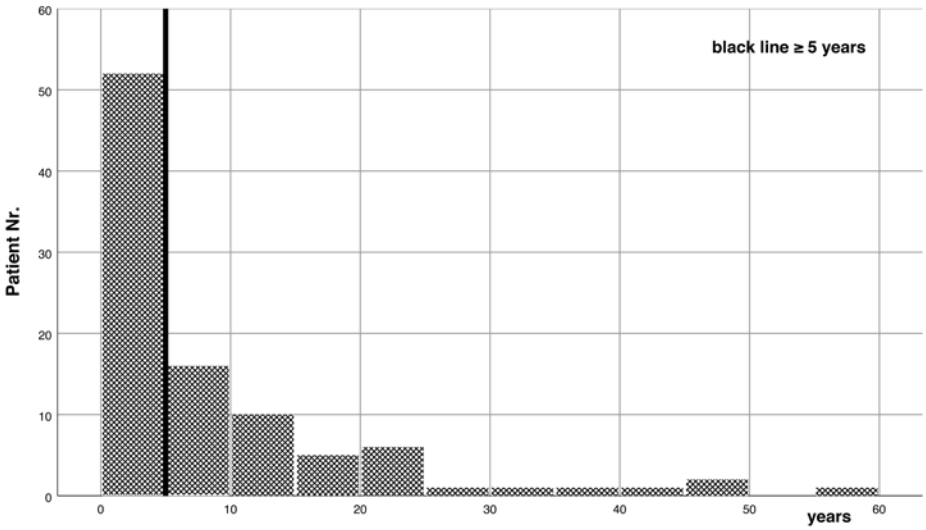

Figure 1. Disease duration from the first Raynaud phenomenon.

Table 2. Clinical characteristics at cutoff < 5 and ≥ 5 years (total N = 96).

	Disease Duration		
	< 5 Years, N = 52	≥ 5 Years, N = 44	*P*
Age, yrs	55 (42–67)	54 (43–64)	0.9
Female	48 (92.3)	39 (88.6)	0.7
RP	52/52 (100)	44/44 (100)	
RP disease duration, yrs	2 (0.6–3)	12 (8–23)	0.000
Puffy fingers (ever)	11/48 (22.9)	6/43 (14.0)	0.3
Digital ulcers (ever)	1/42 (2.4)	5/37 (2.7)	1.0
Pitting scars (ever)	0/43	2/37 (5.4)	0.2
mRSS	0 (0–0)	0 (0–0)	0.2
Musculoskeletal			
Joint synovitis	8/54 (15.4)	4/44 (9.1)	0.4
Tendon friction rubs	1/52 (1.9)	0/44	1.0
Cardiopulmonary			
Lung fibrosis on chest HRCT	1/42 (4.8)	2/35 (5.7)	1.0
FVC < 80%	4/46 (8.7)	3/40 (7.5)	1.0
DLCO < 70%	5/47 (10.6)	2/40 (5.0)	0.4
Dyspnea			
Stage 1	41/47 (87.2)	34/39 (87.2)	0.5
Stage 2	6/47 (12.8)	5/39 (12.8)	0.5
Gastrointestinal			
Esophageal symptoms	12/50 (24.0)	15/43 (35.7)	0.2
Renal crisis	0/50	0/43	1.0
Laboratory markers			
ANA	47/50 (94.0)	42/43 (97.7)	0.6
ACA	23/50 (46.0)	20/43 (46.5)	1.0
Anti-Scl70	1/50 (2.0)	0/43	1.0
Anti-U1RNP	2/46 (4.3)	1/43 (2.3)	1.0
Anti-RNA polymerase III	2/48 (4.2)	3/42 (7.1)	0.7
CK elevation	6/50 (12)	6/43 (14.0)	0.8
Proteinuria	3/50 (6.0)	0/42 -	0.2
ESR > 25 mm/h	3/46 (6.5)	2/41 (4.9)	1.0
CRP elevation	3/48 (6.3)	2/43 (4.7)	1.0
Immunosuppressive treatment†	2/52 (3.8)	0/44	0.5
Abnormal NFC	34/48 (70.8)	32/39 (82.1)	0.2
Telangiectasia	8/43 (18.6)	5/37 (13.5)	0.5

For categorical variables, the absolute and relative frequencies are expressed as n/total valid cases (%). Continuous variables are expressed as median (IQR). † Immunosuppressive treatment is defined as prednisone ≥ 10 mg/day or any treatment with disease-modifying antirheumatic drugs or biologics. For 6/102 patients, information on disease duration since first RP symptom was missing, and these 6 patients were excluded from this analysis. ACA: anticentromere antibodies; ANA: antinuclear antibodies; anti-Scl70: anti-topoisomerase I antibodies; CK: creatine kinase; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; HRCT: high-resolution computed tomography; mRSS: modified Rodnan skin score; NFC: nailfold capillaroscopy; NYHA: New York Heart Association; RP: Raynaud phenomenon.

This needs to be considered in clinical practice and study design of patients with early SSc.

REFERENCES

1. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-15.
2. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518-28.
3. Jordan S, Maurer B, Toniolo M, Michel B, Distler O. Performance of the new ACR/EULAR classification criteria for systemic sclerosis in clinical practice. Rheumatology 2015;54:1454-8.
4. Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM 2010;103:109-15.
5. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet 2017;389:2338-48.
6. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: Results of a Delphi consensus study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis 2011;70:476-81.
7. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G,

Czirják L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis 2014;73:2087-93.
8. Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. PLoS One 2016;11:e0163894.
9. Guiducci S, Bellando-Randone S, Matucci-Cerinic M. A new way of thinking about systemic sclerosis: the opportunity for a very early diagnosis. Isr Med Assoc J 2016;18:141-3.
10. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/EULAR collaborative initiative. Arthritis Rheum 2013;65:2737-47.
11. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2013;72:1747-55.
12. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association diagnostic and therapeutic criteria committee. Arthritis Rheum 1980;23:581-90.
13. Bellando-Randone S, Matucci-Cerinic M. Very early systemic sclerosis and pre-systemic sclerosis: definition, recognition, clinical relevance and future directions. Curr Rheumatol Rep 2017;19:65.
14. 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 2014;73:1340-9.
15. Walker JG, Steele RJ, Schnitzer M, Taillefer S, Baron M, Canadian Scleroderma Research Group, et al. The association between disease activity and duration in systemic sclerosis. J Rheumatol 2010;37:2299-306.
16. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000; 43:2437-44.
17. Bruni C, Guiducci S, Bellando-Randone S, Lepri G, Braschi F, Fiori G, et al. Digital ulcers as a sentinel sign for early internal organ involvement in very early systemic sclerosis. Rheumatology 2015;54:72-6.
18. Maurer B, Graf N, Michel BA, Müller-Ladner U, Czirják L, Denton CP, et al. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. Ann Rheum Dis 2015;74:1124-31.
19. Dobrota R, Maurer B, Graf N, Jordan S, Mihai C, Kowal-Bielecka O, et al. Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: A EUSTAR analysis. Ann Rheum Dis 2016;75:1743-8.
20. Lepri G, Guiducci S, Bellando-Randone S, Giani I, Bruni C, Blagojevic J, et al. Evidence for oesophageal and anorectal involvement in very early systemic sclerosis (VEDOSS): report from a single VEDOSS/EUSTAR centre. Ann Rheum Dis 2015; 74:124-8.