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Very Early Diagnosis of Systemic Sclerosis in Clinical Practice – Case Report and Review of the Literature

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SUMMARY Systemic sclerosis (SSc) is a systemic autoimmune disease characterised by generalized microangiopathy and fibrosis of skin and internal organs. The 2013 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) criteria have contributed considerably to classifying patients with SSc in earlier stages, but they still lack sensitivity for a very early stage of the disease. Criteria for a very early diagnosis of SSc (VEDOSS) have been proposed by EULAR Scleroderma Trial and Research group (EUSTAR) which include three red flags: Raynaud's phenomenon, puffy fingers and antinuclear antibody positivity, plus SSc specific antibodies positivity and/or abnormal nailfold capillaroscopy.
We report a case of a 54-year-old female patient with 6-week history of puffy fingers, Raynaud phenomenon and positive antinuclear antibodies. Further workup revealed early pathologic capillary pattern by nailfold capillaroscopy and positive anticentromere antibodies. Screening for internal organ involvement detected no heart, lung, or upper gastrointestinal tract involvement. The patient was started on pentoxifylline with further follow-up.
The aim of the implementation of VEDOSS criteria is to diagnose SSc at the earliest possible stage, so that subclinical internal organ involvement could be detected and appropriate treatment started at a potentially reversible stage.

KEY WORDS: Systemic sclerosis, Raynaud phenomenon, antibodies, antinuclear

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by generalized small vessel vasculopathy and fibroblast dysfunction leading to fibrosis of the skin and internal organs. The clinical manifestations and prognosis are variable, depending on the extent of internal organ involvement. The disease is generally associated with significant disability and increased mortality. Some subsets of SSc can be identified: limited cutaneous SSc, diffuse cutaneous SSc, and SSc without skin involvement (1,2). The prognosis is significantly worse and mortality is higher in the subset of patients with diffuse cutaneous SSc compared with limited cutaneous SSc, and in patients with lung, heart, and kidney involvement (3).

In the absence of a diagnostic test, and given the clinical heterogeneity of SSc and the need for consistency across different centers, several classification criteria have been developed for research purposes (4-6). The 1980 American College of Rheumatology

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(ACR) criteria (formerly American Rheumatism Association) (4) perform poorly in identifying subjects in the early stages of the disease, as well as subjects with no skin lesions beyond the fingers, no finger ulcers, and no interstitial lung disease (ILD). Advances in knowledge about SSc and the availability of diagnostic tests including SSc-specific autoantibodies and nailfold capillaroscopy (NC) have led to the development of the new 2013 ACR and European League Against Rheumatism (EULAR) classification criteria for SSc (6). Although these criteria have contributed considerably to classifying patients as definite SSc earlier in the course of disease, they still lack the sensitivity required for the very early stage of SSc (7-9).

EUSTAR (EULAR Scleroderma Trial and Research group) has proposed new criteria for a very early diagnosis of SSc (VEDOSS), that are being validated. These preliminary criteria include three red flags – Raynaud's phenomenon (RP), puffy fingers, and antinuclear antibody (ANA) positivity, plus SSc-specific antibodies positivity (anti-centromere antibodies (ACA) or anti-topoisomerase-1 antibodies) and/or abnormal nailfold capillaroscopy (10).

The aim of this paper was to stress the importance of diagnosing SSc at a very early stage, before the occurrence of clinically significant and irreversible organ damage.

CASE REPORT

A 54-year-old female patient presented with a 6-week history of puffy fingers and RP. The medical history was unremarkable, except multinodular euthyroid goiter and occasional mild and transient photosensitive rashes. The family history was negative for rheumatologic diseases.

The physical examination revealed puffy fingers (Figure 1) with no other remarkable findings. No digital ulcerations or pitting scars, and no signs of synovitis were found. Immunology tests revealed positive ANA with a centromere pattern in indirect immunofluorescence (IIF). Antibodies to double-stranded DNA (dsDNA) and extractable nuclear antigen (ENA) panel were negative, and the serum levels of C3 and C4 complement components were normal. Erythrocyte sedimentation rate and serum level C-reactive protein were normal. Complete blood count and routine serum biochemistry values were in the reference range.

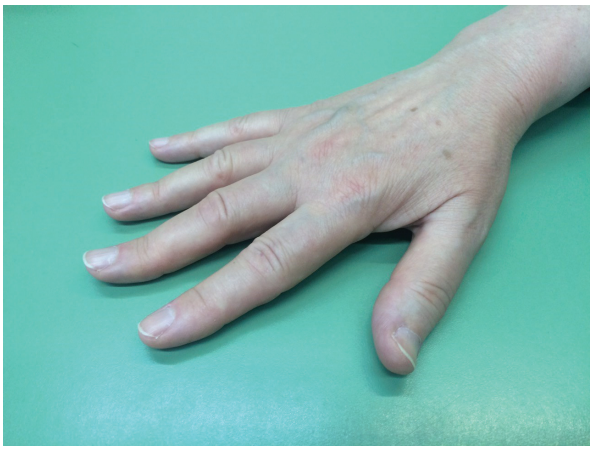

Figure 1. Puffy fingers.

At that point, all three VEDOSS red flags were present. Additional immunology tests detected a high titer of ACA. NC revealed megacapillaries in two of eight inspected nail folds, and a single capillary hemorrhage – an early pathologic SSc pattern (Figure 2). Musculoskeletal ultrasound showed no signs of synovitis. The patient was ultimately diagnosed with very early SSc.

As the patient reported no gastrointestinal or respiratory symptoms, further tests were performed to screen for subclinical internal organ involvement. Upper gastrointestinal (GI) endoscopy revealed chronic gastritis with negative Helicobacter pylori on biopsy samples. Pulmonary function tests (spirometry and carbon-monoxide diffusing capacity) were normal. High-resolution computed tomography (HRCT) showed no signs of interstitial lung disease. The electrocardiogram was normal, and echocardiography detected no signs of heart abnormalities as well as no indirect signs of pulmonary hypertension.

Based on the normal HRCT scan results (chest and upper abdomen) and an unremarkable gynecological examination, we excluded occult neoplasm and possible paraneoplastic syndrome. In addition, no skin thickening was present on clinical examination that would suggest the presence of a scleroderma-like disorder.

We recommended treatment with amlodipine and pentoxiphylline for RP, but the patient was reluctant to start medication at the time.

At follow-up six months after the initial presentation, pulmonary function tests, electrocardiogram examination, and echocardiography were repeated, and no pathology was detected once again. NC findings were also unchanged. The patient was then started on pentoxifylline 400 mg daily, and the dose was increased to 800 mg daily 10 days later. At next follow-up 12 months after the diagnosis, puffy fingers were still present on physical examination, and there were still no signs of sclerodactyly, pitting scars or digital ulcers, or skin thickening elsewhere. The same diagnostic tests were repeated, except for NC, and no

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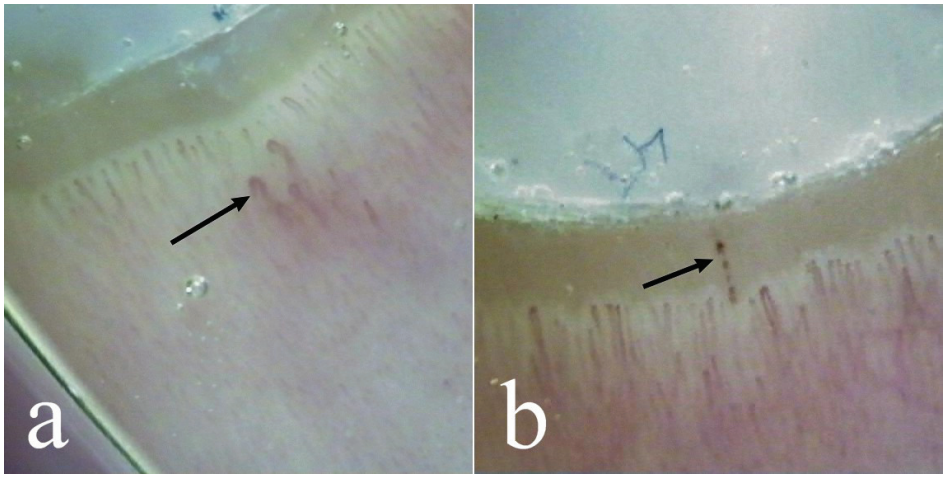

Figure 2. Nailfold capillaroscopy: (a) megacapillaries (arrow); (b) capillary hemorrhage (arrow) and a few dilated capillaries. Magnification ×10.

signs of lung or heart involvement were found. Further treatment with pentoxifylline and further close follow-up were recommended.

DISCUSSION

SSc is a clinically heterogeneous disease with a still unpredictable clinical course. Its mortality rate has not changed significantly over the past 4 decades (11). Despite advancements in treatment, pulmonary manifestations comprising ILD and pulmonary arterial hypertension (PAH) are presently the main cause of death in patients with SSc. Screening and diagnostic tests, both non-invasive and invasive, are widely available today. Early diagnosis and treatment are essential for improving patient outcomes (12,13). The poor prognosis of SSc reflects the absence of currently available drugs to counteract the fibrotic process (14). Novel targeted therapies are currently being investigated that might be particularly promising in early inflammatory stages of SSc (15,16).

Very early stages of SSc are clinically characterized by the onset of RP and puffy fingers, later turning into sclerodactyly. However, these features are not specific for SSc, as they can also be present in other entities (17). SSc-specific autoantibody positivity and nailfold capillaroscopy abnormalities have been shown to indicate a very high probability of developing definite SSc in patients with RP. Koenig et al. conducted a prospective study showing that patients with RP who had both of these predictors at baseline were 60 times more likely to develop definite SSc according to the ACR criteria (18). Recently, Bissell et al. found that the detection of a SSc nailfold capillaroscopy pattern in patients with RP had a sensitivity of 71%, specificity of 95%, positive predictive value of 84%, and negative predictive value of 90% for identifying patients who fulfilled either VEDOSS or 2013 ACR/EULAR criteria for SSc (19). Furthermore, the EUSTAR group demonstrated that puffy fingers is an important predictor of SSc in patients with RP and positive ANA, while its relevance in patients with ANA negative RP still requires further clarification (20). At present, the criteria for VEDOSS proposed by EUSTAR are provisional and need to be validated by prospective studies (10).

Microvascular abnormalities are a key feature of SSc and are central to its pathogenesis (14). Della Rossa *et al.* evaluated post-occlusive reactive hyperemia by laser speckle contrast analysis in patients with SSc, as an estimate of microvascular damage. The authors found a significant difference in the post-ischemic hyperemic peak flow between VEDOSS and established patients with SSc, indicating a different pattern of vascular involvement in these successive stages of the disease (21).

The aim of the implementation of VEDOSS criteria in clinical practice is to detect SSc at the earliest possible stage, before the development of irreversible fibrosis and organ damage, so that timely screening for subclinical internal organ involvement can be performed and appropriate treatment started at a potentially reversible stage – the "window of opportunity" (9,14).

Screening for internal organ involvement was performed in our patient, who fulfilled the VEDOSS criteria. Clinical examinations and diagnostic workup for up to 12 months after the diagnosis detected no signs of pulmonary or cardiac involvement. Nevertheless, it is important to note that the gastrointestinal tract was assessed only with esophagogastroscopy. Esophageal manometry was not performed, and thus esophageal motility disorder at a stage before the development of gastro-esophageal reflux disease

could not be excluded in the otherwise asymptomatic patient. Further careful and comprehensive follow-up at regular intervals is required.

The esophagus is the most commonly affected part of the gastrointestinal tract in patients with SSc, followed by the anorectum. Lepri *et al.* showed that esophageal and anorectal involvement, as assessed with manometry, is present in the majority of patients with VEDOSS, and that lung involvement is also already detectable in some of these patients (22). Furthermore, Bruni *et al.* reported a statistically significant association between digital ulcers and esophageal manometry alteration in patients with VEDOSS. Since no digital ulcers were observed in patients without internal organ involvement, the authors suggested that digital ulcers may be a sentinel sign for early organ involvement in patients with VEDOSS (23).

CONCLUSION

The treatment of SSc remains challenging for clinicians, and despite certain advancements, the prognosis of the disease is still generally unfavorable. The validation of the VEDOSS criteria and their implementation into clinical practice would allow for the detection of organ impairment at a subclinical and potentially reversible stage – the window of opportunity – during which more benefit from immunosuppressive therapy may be derived. Currently, novel targeted therapies are being investigated, which might be promising in the future especially if applied early enough in the course of disease.

We presented a patient with RP and puffy fingers who fulfilled the VEDOSS criteria. During one year of follow-up, no progression of physical signs or detectable signs of lung and heart involvement were observed.

The predictors of progression and severity in SSc still remain unknown, and future prospective studies are needed to identify patients who might benefit from more aggressive treatment.

References:

1. Wollheim FA. Classification of systemic sclerosis: visions and reality. Rheumatology (Oxford). 2005;44:1212-6.
2. Assassi S, Del Junco D, Sutter K, McNearney TA, Reveille JD, Karnavas A, *et al.* Clinical and genetic factors predictive of mortality in early systemic sclerosis. Arthritis Rheum. 2009;61:1403-11.
3. Ferri C, Valentini G, Cozzi F, Sebatiani M, Michelassi C, La Montagna G, *et al.* Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore). 2002;81:139-53.
4. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommitee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23:581-90.
5. LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28:1573-76.
6. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, *et al.* Classification Criteria for Systemic Sclerosis: An ACR-EULAR Collaborative Initiative. Arthritis Rheum. 2013;65:2737-47.
7. 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 (Oxford). 2015;54:1454-8.
8. Sáez-Comet L, Simeón-Aznar CP, Pérez-Conesa M, Vallejo-Rodríguez C, Tolosa-Vilella C, Iniesta-Arandia N, *et al.* Applying the ACR/EULAR Systemic Sclerosis Classification Criteria to the Spanish Scleroderma Registry Cohort. J Rheumatol. 2015;42:2327-31.
9. Bellando-Randone S, Guiducci S, Matucci-Cerinic M. Very early diagnosis of systemic sclerosis. Pol Arch Med Wewn. 2012;122 Suppl 1:18-23.
10. 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.
11. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford). 2012;51:1017-26.
12. Cappelli S, Bellando Randone S, Camiciottoli G, De Paulis A, Guiducci S, Matucci-Cerinic M. Interstitial lung disease in systemic sclerosis: where do we stand? Eur Respir Rev. 2015;24:411-9.
13. Chaisson NF, Hassoun PM. Systemic sclerosis-associated pulmonary arterial hypertension. Chest. 2013;144:1346-56.
14. Elhai M, Avouac J, Kahan A, Allanore Y. Systemic sclerosis: Recent insights. Joint Bone Spine. 2015;82:148-53.
15. Sakkas LI, Simopoulou T, Katsiari C, Bogdanos D,

Chikanza IC. Early systemic sclerosis-opportunities for treatment. Clin Rheumatol. 2015;34:1327-31.

16. Distler O, Cozzio A. Systemic sclerosis and localized scleroderma-current concepts and novel targets for therapy. Semin Immunopathol. 2016;38:87-95.
17. Anna Kuryliszyn-Moskal, Jacek Kita, Anna Hryniewicz. Raynaud's phenomenon: new aspects of pathogenesis and the role of nailfold videocapillaroscopy. Reumatologia. 2015;53:87-93.
18. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, *et al.* Autoantiboides and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum. 2008;58:3902-12.
19. Bissell LA, Abignano G, Emery P, Del Galdo F, Buch MH. Absence of Scleroderma pattern at nail fold capillaroscopy valuable in the exclusion of Scleroderma in unselected patients with Raynaud's Phenomenon. BMC Musculoskelet Disord. 2016;17:342.
20. 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.
21. Della Rossa A, D'Ascanio A, Barsotti S, Stagnaro C, Mosca M. Post-occlusive reactive hyperaemia (POHR) in systemic sclerosis: very early disease (VEDOSS) represents a separate entity compared to established disease. Scand J Rheumatol. 2016;45:408-11.
22. 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.
23. 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 (Oxford). 2015;54:72-6.