Cardiac involvement, a threatening very early manifestation of systemic sclerosis: evidence from VEDOSS patients

Sirs,
Early diagnosis of systemic sclerosis (SSc) is crucial for a prompt identification of organ involvement and for an early treatment (1). The preliminary criteria for the very early diagnosis of SSc (VEDOSS) were developed in 2011 (2, 3). While gastro-intestinal involvement (4) and digital ulcers (5) have already been described in VEDOSS patients, cardiac involvement characterisation is still lacking. Of note, a recent study has highlighted that diffuse myocardial fibrosis is already present in VEDOSS patients (6). Nonetheless, the pathogenesis of myocardial involvement in SSc include also microvascular damage and myocardial inflammation (6-8). Herein, we report three VEDOSS patients with different manifestations of SSc-related heart involvement, emphasising the importance of all the three early SSc-related pathogenic mechanisms.

Clinical case 1: vasculopathy. A 45-year-old female with Raynaud's phenomenon (RP), was evaluated for exertional dyspnoea and atypical chest pain. Blood tests including cardiac biomarkers, cardiac stress test, coronary CT scan (CCT) and CMR were negative, whereas cardiopulmonary exercise test was stopped due to the occurrence of dyspnoea and T-wave changes. At rheumatological evaluation the presence of puffy fingers, anti-topoisomerase-I positivity, and active-late scleroderma pattern at NVC were detected. Chest high-resolution CT (HRCT) and pulmonary function tests (PFTs) were normal. A VEDOSS diagnosis was made. Myocardial perfusion SPECT with adenosine stress showed moderate-grade defects suggestive of stress-ischaemia (Fig. 1A). Verapamil, acetylsalicylic acid and hydroxychloroquine were started. RP, dyspnoea and episodes of chest pain improved.

Clinical case 2: inflammation. A 38-year-old female was admitted for acute chest pain. 12-lead ECG revealed non-specific T-wave changes. NTproBNP(309 pg/mL) and troponin T(TnT)(189 ng/L) serum levels were raised; while echocardiography was normal. 24h-ECG-Holter recorded 3524 ventricular ectopic beats (VEBs). Systemic inflammatory markers and CPK were normal. CCT was negative while CMR disclosed T2-hyperintensity, increased T2 mapping, late gadolinium enhancement (LGE) areas and depressed LVEF (52%). Endomyocardial biopsy (EMB) was performed. In the meanwhile, the patient experienced the first occurrence of RP and puffy fingers. Anti-CENP-B antibodies positivity and early scleroderma pattern at NVC were detected. HRCT and PFTs were normal. A VEDOSS diagnosis was made.
EMB showed a chronic-active virus-negative myocarditis with lymphocytic infiltrate, interstitial oedema and myocyte necrosis (Fig. 1B). Steroids and mycophenolate were started with benefit on chest pain and TnT and NT-proBNP normalisation. After 12 months, a significant reduction in VEBs (165/24h) was recorded and a CMR showed normal LVEF (58%), resolution of myocardial oedema, while LGE areas remained unchanged.

Clinical case 3: fibrosis. A 39-year-old female was resuscitated after sustained ventricular fibrillation (S-VF). Severe LVEF impairment (35%) with normal CCT was detected. CMR disclosed extensive areas of LGE with slight oedema. The patient was treated with ACE-inhibitor, beta-blocker and cardioverter defibrillator (ICD) implantation. LVEF improved (51%) but further S-VF episodes were recorded. EMB revealed extensive myocardial fibrosis with no inflammatory infiltrates (Fig. 1C). Additional ICD shocks were recorded. CMR was repeated but it was inconclusive therefore a 18F-fluoro-deoxy-glucose PET was performed and it showed increased myocardial uptake in the septum. A subsequent EMB confirmed only extensive fibrotic replacement without inflammation.
At rheumatologic evaluation the presence of RP, puffy fingers, early scleroderma pattern at NVC, and anti-RNA polymerase III positivity. A diagnosis of VEDOSS with myocardial fibrosis was made. Immunosuppressive therapy with mycophenolate was started with no improvement as the arrhythmic burden remained refractory to medical therapy.
Our cases suggest that even in VEDOSS patients, heart involvement may occur with different clinical manifestations linked to the three main SSc pathogenetic events: microvascular abnormalities, tissue inflammation and fibrosis. Since the majority of the VEDOSS patients progress to definite SSc (9, 10), they represent the ideal population for early organ assessment. How and when is yet to be defined for VEDOSS patient but it should be strongly encouraged to prevent irreversible cardiac damage.

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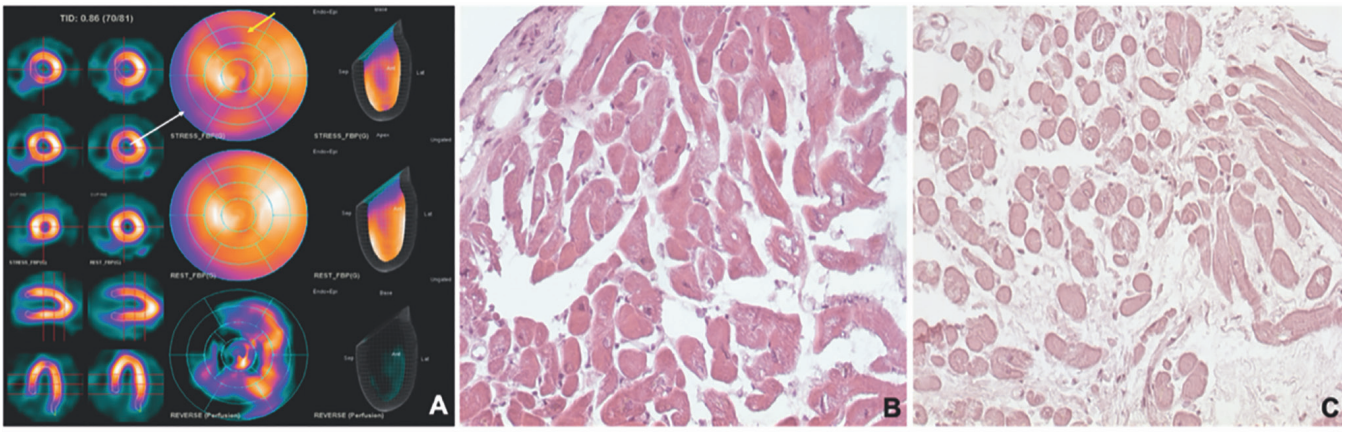

Fig. 1. A: Rest and adenosine stress myocardial perfusion images obtained 99mTC-tetrafosmin as the perfusion tracer in a 45-year-old VEDOSS patient. Images are displayed in short axis (top), horizontal long axis (middle) and vertical long axis (bottom) of the heart with the stress images on the top of each pair. Images after stress showed moderate-grade defects at the level of the mid and apical segments of the anterior wall (yellow arrow) of left ventricle, and the mid and basal infero-septal segments indicative of stress ischaemia (white arrow). **B**: Histological findings on endomyocardial biopsy of a 38-old VEDOSS patient with chronic-active myocarditis. On histology, endomyocardial biopsy showed lymphomonocytic infiltration with myocyte necrosis (H&E); on immunostaining, the inflammatory infiltrate was composed of lymphocytes CD3+ (CD3+ > 7/mm^2) and macrophages CD68+ (not shown). **C**: Histological findings on endomyocardial biopsy of a 39-old VEDOSS patient with myocardial fibrosis. On histology, endomyocardial biopsy showed extensive replacement and interstitial fibrosis without lymphomonocytic infiltration.

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