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Cardiovascular magnetic resonance imaging pattern at the time of diagnosis of treatment naïve patients with connective tissue diseases

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ABSTRACT

Background-aim: Cardiac involvement at diagnosis of connective tissue disease (CTD) has been described by echocardiography. We hypothesized that cardio-vascular magnetic resonance (CMR) detects occult lesions at CTD diagnosis.

Patients-methods: CMR was performed early after diagnosis in 78 treatment-naïve CTDs (aged 43 ± 11, 59F/19M) without cardiac involvement [5 Takayasu arteritis (TA), 4 Churg Strauss syndrome (CSS), 5 Wegener granulomatosis (WG), 16 systemic lupus erythematosus (SLE), 12 rheumatoid arthritis (RA), 8 mixed connective tissue diseases (MCTD), 12 ankylosing spondylitis (AS), 3 polymyalgia rheumatica (PMR), 8 systemic sclerosis (SSc) and 5 dermatomyositis (DM)]. Acute and chronic lesions were assessed by T2 > 2 with positive LGE and T2 < 2 with positive LGE, respectively.

Results: In 3/5 TA, 3/4 CSS, 4/5 WG, 10/16 SLE, 9/12 RA, 6/8 MCTD, 4/12 AS, 1/3 PMR, 2/8 SSc and 2/5 DM, the T2 ratio was higher compared to normal (2.78 ± 0.25 vs 1.5 ± 0.2, $p < 0.01$). Myocarditis was identified in 1 TA, 1 SLE, 1 RA, 1 SSc and 2 DM patients; diffuse, subendocardial fibrosis in 1 CSS and 1 RA patient, while subendocardial myocardial infarction in 3 SLE, 1 MCTD, 1 PMR and 2 RA patients. CMR re-evaluation after 6 and 12 months of rheumatic and cardiac treatment, available in 28/52 CTDs with increased T2 ratio, showed significant improvement in T2 ratio ($p < 0.001$), non-significant change in LGE extent and normalisation of those with impaired LV function.

Conclusions: Occult CMR lesions, including oedema, myocarditis, diffuse subendocardial fibrosis and myocardial infarction are not unusual in treatment naïve CTDs and may be reversed with appropriate treatment.

1. Introduction

Although cardiovascular comorbidities vary greatly between patients with connective tissue diseases (CTD), they do confer a high risk of morbidity and mortality in this population [1]. CTD patients may present with disease-associated heart involvement at any stage during the course of their disease [1]. Cardiovascular involvement has been observed in 70% of patients, evaluated at the early stages of CTD and identification of such involvement was useful for both diagnosis and management of these patients [2]. However, these data came from a limited spectrum of CTDs, predominantly systemic lupus erythematosus (SLE), mixed connective tissue diseases (MCTD) and systemic sclerosis (SSc). Additionally, cardiac evaluation was performed by echocardiography, an operator depended technique [2].

Cardiovascular magnetic resonance (CMR), a non-invasive, non-radiating, operator independent technique also capable of performing tissue characterization, holds the promise for early diagnosis of cardiovascular disease in CTD patients. CMR has already been used for the evaluation of several systemic autoimmune disorders [1,3,4]. Raman et al. described the typical CMR pattern of heart involvement in vasculitides [5], while Fayad et al. also emphasized that subclinical vasculitis

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can be a potential explanatory mechanism behind the increased cardiovascular risk seen in rheumatoid arthritis (RA) patients [6]. Recently, a consensus regarding the use of CMR in the evaluation of CTDs has been published by a working group of specialists in Cardiology and Rheumatology [7]. However, the pattern of cardiovascular involvement, as seen in CMR evaluation of treatment-naïve CTD patients at the time of diagnosis, has not been described.

Assessment of myocardial oedema by CMR represents a new, robust diagnostic tool in the field of cardiology, seeing as even endomyocardial biopsy is unable to reliably detect its presence [8]. Extensive studies have confirmed a close correlation between T2 and oedema [9]. By adding T2 to a standard CMR protocol (function, perfusion, and scar), the specificity, positive predictive value and overall accuracy for the detection of an acute coronary syndrome increased from 84% to 96%, 55% to 85%, and 84% to 93%, respectively [10]. Furthermore, fibrosis as assessed by LGE not only detects myocardial scar in as little as 1 cm^3 of tissue, substantially less than other in vivo techniques, but has also an excellent agreement with histology in both animals and humans [11,12]. CMR was also proven useful in detecting small subendo-subepi- and/or intra-myocardial scars and diffuse, subendocardial fibrosis, missed by other imaging techniques [1]. Even an area of LGE < 2% of LV mass was associated with a >7-fold increase in risk for a major adverse cardiac event [13].

We hypothesized that CMR has the potential to detect asymptomatic cardiovascular involvement at the time of CTD diagnosis. The aim of our study was to prospectively evaluate the possibility of asymptomatic cardiovascular disease presence in treatment-naïve patients with recently diagnosed CTD through the use of CMR.

2. Patients-methods

2.1. Patients

A population of 78 treatment-naïve CTD patients (aged 43 ± 11.5, 59F/19M) without any evidence of cardiac involvement (normal medical history, physical examination, ECG and echocardiogram) was evaluated with CMR 7–10 days after the diagnosis of CTD. It consisted of 5 patients with Takayasu arteritis (TA), 4 with Churg Strauss syndrome (CSS), 5 with Wegener granulomatosis (WG), 16 with SLE, 12 with RA, 8 with MCTD, 12 with ankylosing spondylitis (AS), 3 with polymyalgia rheumatica (PMR), 8 with SSc, and 5 with dermatomyositis (DM). CMR was also performed in 20 healthy individuals. Characteristics of each group of CTD patients are presented in Table 1. No participants had been commenced on any immunosuppressive or cardiovascular treatment at the time of cardiac function evaluation. The patient population was compared with an age and sex-matched control group. Written consent was obtained from all participants (patients and controls) and the protocol was approved by the Hospital's Ethics Committee.

Patients underwent a thorough baseline evaluation including a detailed review of their medical history and hospital records, physical examination and blood tests. All medications and their indication were also recorded. Laboratory examinations included inflammatory markers, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as cardiac troponin T (cTnT) and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP), as biochemical indices of subclinical heart involvement. Clinical and CMR characteristics of CTD patients at the time of disease diagnosis are presented in Table 2. For those with abnormal CMR findings, a second CMR scan after 6 months of treatment and a third after one year of treatment was scheduled (Fig. 1).

Immediately after evaluation with CMR, in patients with TA oral treatment with steroids 1 mg/kg daily was started, tapered over time as symptoms subsided. For patients whose disease was steroid resistant or relapsing, methotrexate was started and continued for at least 1 year after remission. In CSS and WG, treatment with prednisone (initiated at 1 mg/kg daily for 1 to 2 months with gradual tapering) and cyclophosphamide (2 mg/kg daily for 6–12 months) was introduced. The following treatments were initiated for each group of CTD patients: in SLE, treatment with glucocorticoids and antimalarials, in RA, NSAIDs, corticosteroids and methotrexate, in MCTD, NSAIDs and hydroxychloroquine, in AS, corticosteroids and anti-TNF treatment (Etanercept), in SSc, corticosteroids and methotrexate, in PM, corticosteroids, and in DM, corticosteroids and methotrexate. Additionally, cardiac medication was started according to ESC guidelines for myocarditis and myocardial infarction with normal LV ejection fraction [14].

3. Methods

3.1. Cardiovascular magnetic resonance imaging

CMR including STIR T2 and late (LGE) gadolinium enhancement was performed in all CTDs with a 1.5 Tesla scanner (Signa CV/i, GE Medical Systems) using ECG-triggered steady-state, free precession [SSFP] breath-hold cines (echo time (TE)/repetition time (TR) 1.6/3.2 ms, flip angle 60) in long-axis planes and sequential 8 mm short-axis slices (3 mm gap) from the atrioventricular ring to the apex.

Dark-blood STIR T2-weighted images (triple inversion recovery; TE: 60 ms, TR: 2 × R–R interval, TI: 170 ms, slice thickness 20 mm, flip angle: 180, pixel size 2.3 × 1.3 mm) were acquired in short-axis planes for oedema imaging. Finally, late gadolinium enhanced (LGE) images were acquired 10 min after intravenous gadolinium-DTPA (Schering;

Table 1
Clinical and immunological characteristics of each group of CTD patients at the time of CMR evaluation.

	TA $N = 5$	CSS $N = 4$	WG $N = 5$	SSc $N = 8$	SLE $N = 16$	RA $N = 12$	MCTD $N = 8$	DM $N = 5$	AS $N = 12$	PR $N = 3$
ENT involvement	0	3	5	0	0	0	0	0	0	0
Eye involvement	0	0	0	0	0	0	0	0	2	1
Lung involvement	0	1	5	7	0	0	0	2	0	0
Bronchial asthma	0	4	0	0	0	0	0	0	0	0
Kidney involvement	0	0	3	1	6	0	0	0		0
GI involvement	0	0	0	5	0	0	0	0	0	0
Noncardiac aneurysm	0	0	0	0	0	0	0	0	0	0
Occlusion of main aortic branches	5	0	0	0	0	0	0	0	0	0
Diminished pulse	5	0	0	0	0	0	0	0	0	0
Asymetrical BP	5	0	0	0	0	0	0	0	0	0
Musculoskeletal involvement	3	1	0	6	10	8	7	5	5	3
Neurologic involvement	2	3	3	2	2	0	0	0	0	0
Skin involvement	0	3	3	8	10	0	5	5	0	0
Raynaud phenomenon	0	0	0	8	0	2	8	2	0	0
Arthritis	0	0	0	4	8	12	5	2	0	1
Positive ANCAs	0	3	5	0	0	0	0	0	0	0
Positive ANA	0	0	0	3	16	0	0	1	0	0
Anti Ro/SSA	0	0	0	0	4	0	0	0	0	0
Anti dsDNA	0	0	0	0	16	0	2	0	0	0
RF	0	2	0	0	0	12	2	0	0	0
ACPA					0	10			0	0
Anti-RNP antibodies	0	0	0	0	0	0	8	0	0	0
Antitopoisomerase antibodies	0	0	0	8	0	0	0	0	0	0
Anticentromere antibodies (ACAs)	0	0	0	0	0	0	0	0	0	0
Anti–Jo-1	0	0	0	0	0	0	0	2	0	0
HLA-B27	0	0	0	0	0	0	0	0	12	0

ACPA = anti–citrullinated protein antibody.
RNP = anti-ribonucleoprotein (RNP) antibodies.
Anti–Jo-1 = antihistidyl transfer RNA [t-RNA] synthetase.

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