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Original Article

Comprehensive evaluation of cardiac involvement in eosinophilic granulomatosis with polyangiitis (EGPA) with cardiac magnetic resonance

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ABSTRACT

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis characterized by hypereosinophilia. EGPA typically develops in three clinical phases, beginning with asthma, followed by tissue eosinophilia and finally systemic vasculitis. Cardiac involvement is the most important predictor of mortality; it occurs in approximately 15–60% of EGPA patients, a significant proportion of whom are asymptomatic and have normal electrocardiogram (ECG) and echocardiogram. Early detection and management of cardiac disease could positevely affect prognosis. Cardiovascular magnetic resonance (CMR) has emerged as the gold standard cardiac imaging technique in the evaluation of cardiomyopathies, due to its ability to reliably assess anatomy, function, and tissue characterization.
Aim: Purpose of this study was to assess the role of CMR in detecting cardiac disease in patients with EGPA in clinical remission.
Methods: A dedicated CMR protocol including functional analysis, and pre and post-contrast tissue characterization was performed in 11 patients with EGPA and the results were compared with 11 healthy subjects.
Results: EGPA patients had lower left ventricular ejection fraction compared to controls (56 ± 19 vs 68.7 ± 5.2, p value 0.02). Late gadolinium enhancement (LGE), representing replacement fibrosis, was positive in 9/11 (82%) patients, mainly with a non-ischemic pattern. In 3/11 (27%) patients a left ventricular thrombus was detected; in 3/11 (27%) patients myocardial edema was detected. CMR parameters of interstitial fibrosis were significantly more elevated in EGPA patients compared to controls.
Conclusions: Patients with EGPA in clinical remission showed a high cardiovascular burden as demonstrated by lower EF, signs of active inflammation, presence of interstitial and replacement fibrosis and intraventricular thrombosis. Further studies on wider populations are warranted to better understand how these findings could impact on prognosis and eventually guide therapy.

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss Syndrome, is a rare systemic vasculitis with an estimated incidence of one per year per one million, characterized by asthma, hypereosinophilia, heart failure, renal damage and peripheral neuropathy. EGPA typically develops in three clinical phases, beginning with asthma, followed by tissue eosinophilia and finally systemic small-vessel vasculitis [1–3]. Cardiac involvement in EGPA is frequent and insidious; it is the most important predictor of mortality and it is detected in over 50% of autopsied EGPA patients [4]. Cardiac manifestations include pericardial effusion, conduction disturbances, pulmonary hypertension, acute coronary syndromes, heart failure and cardiogenic shock [5]. Intraventricular thrombosis can also be present and cause cerebral embolysm. Cardiac disease in EGPA tends to occur in the early phase but it can also occur late in the course of disease.

Cardiovascular magnetic resonance (CMR) has emerged as the gold standard cardiac imaging technique in the evaluation of cardiomyopathies, due to its ability to reliably assess anatomy, function and tissue characterization. Despite clinical remission, normal ECG and echocardiogram, non-ischemic LGE lesions without signs of myocarditis have been described in EGPA patients [6,7]. LGE technique allows the identification of areas of gross fibrosis [8], which can be clearly distinguished from areas of normal myocardium, while it cannot identify the presence of diffuse myocardial fibrosis, a subtle pathologic process involving the entire myocardium and with a potential adverse prognostic significance [9,10]. Recent advances in CMR allow an indirect estimation of diffuse myocardial fibrosis using the T1-mapping technique [11]. Pre-contrast

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(native) T1-mapping is highly sensitive to myocardial water, detecting myocardial oedema, but it is also sensitive to myocardial fibrosis [12]. After contrast administration, post-contrast T1-mapping images can also be acquired. Calibrating pre and post-contrast T1-mapping with blood hematocrit, the extracellular volume fraction (ECV) of the myocardium can be calculated. Both pre- and post-contrast T1-mapping have been shown to correlate well with histological indices of myocardial fibrosis. Myocardial T1-mapping is increasingly being applied to study cardiomyopathies and it has recently been evaluated in patients with different forms of autoimmune disease, showing subtle expansion of myocardial ECV, indicating interstitial remodeling [13–15].

1. Aim

Purpose of this study was to assess the role of CMR in detecting cardiac disease, including the presence of diffuse fibrosis, in patients with EGPA in clinical remission.

2. Methods

Eleven patients with EGPA underwent CMR between March 2010 and October 2015 at Niguarda Hospital in Milan, Italy. The study was performed in accordance with the declaration of Helsinki and informed consent was obtained from each patient. The diagnosis of EGPA was formulated according to the American College of Rheumathology (ACR) criteria [16]. CMR was performed in patients considered to be in clinical remission, defined as absence of any clinical manifestation of EGPA, except asthma or neurological sequelae, at a 6-month follow-up. All patients were followed up at the Department of Allergology and Immunology, which is a regional referral center for EGPA Disease, at Niguarda Hospital in Milano, Italy.

Imaging results were compared with a control group of 11 healthy subjects matched for age and gender. All controls showed a low probability of heart disease after anamnestic and physical examination and evaluation of risk factors; all controls had normal ECG [17].

All patients in the healthy control group had normal hemoglobin (>13 g/dl) and normal renal function (GFR > 90 ml/min).

CMR findings of EGPA patients with a CMR left ventricular-ejection fraction (LVEF) ≥60% or <60% were also compared, according to normal CMR reference values [18].

2.1. CMR protocol

Each patient had been scheduled for contrast-enhanced CMR after the exclusion of contraindications to CMR and gadolinium-based contrast agents, including ferromagnetic implants, claustrophobia and severe renal dysfunction (glomerular filtration rate <30 ml/min/sqm, MDRD equation). CMR scans were performed on a 1.5 T clinical scanner (Siemens Avanto©, Erlangen, Germany) using a four-element phased-array receiver coil. All images were acquired with retrospective ECG gating and during repeated single breath-holds. Balanced steady-state free precession cine images were acquired in three long-axis planes and in contiguous short-axis slices from the atrio-ventricular groove to the apex. T2-weighted CMR was performed with the black-blood short-tau inversion recovery (STIR) sequence in long and short axis planes matching with cine images. Myocardial T1 was determined using a modified MOLLI sequence consisting of 3 inversion blocks generating 3–3-5 single-shot True-FISP images. Pre- and post-Gadolinium (GD) injection short-axis T1 maps were acquired within single breath-holds. LGE images were acquired in long and short-axis planes matching with cine images starting 10 min after intravenous injection of gadobutrol (Bayer©, Germany; 0.15 mmol/kg) and using a segmented inversion-recovery gradient echo sequence or a two-dimensional phase-sensitive inversion-recovery (PSIR) segmented gradient echo MR sequence in the cardiac short and long-axis planes [19].

2.2. CMR data analysis

Left and right ventricular end-diastolic and end-systolic volumes, ejection fraction and left ventricular mass were quantified from short-axis cine images by standard methods using Argus software (Siemens, Erlangen, Germany). Ventricular volumes and mass were indexed to body surface area. Myocardial T1 values (ms) were drawn from AHA 16 regions of the left ventricle avoiding areas with coarse LGE or artifacts. Myocardial pre- and post-contrast T1 values were normalized to the T1 of blood and hematocrit to calculate the Extra Cellular Volume fraction (ECV) [20]. The dichotomous presence or absence of myocardium LGE was determined. LGE distribution within the LV wall was classified as: infarct-typical lesions with subendocardial involvement with variable degrees of transmurality, with coronary artery territory distribution (ischemic pattern); focal intramyocardial or epimyocardial enhancing areas (non-ischemic pattern).

3. Statistics

Statistical analyses were performed using R software. CMR results are expressed as mean ± standard deviation. All dimensional CMR measurements are standardized for body surface area. Continuous data are presented as mean ± SD and categorical data are presented as number and percentage. The differences of the mean of continuous variables of EGPA patients and control subjects have been compared by using the exact Fisher-Pitman permutation test. All the performed statistical tests are one-tailed and a p-value $p < 0.05$ was chosen to establish statistical significance.

4. Results

11 patients with EGPA were compared with 11 healthy subjects; there were not significant differences in age (50.5 ± 15 vs 45 ± 10 years, p = ns) and gender (male/female ratio 6/11 vs 7/11 respectively, p = ns) between the two groups. Patients with EGPA had normal hemoglobin, hematocrit and renal function (Table 1). The only ANCA-positive patient had ear-nose-throat (ENT) manifestations and mild LVEF depression with positive LGE at CMR. The most common clinical manifestations in the acute phase of the disease were respiratory (9/11, 82%), cardiac (1/11, 9%) and neurologic (1/11, 9%). After the diagnosis of EGPA all patients had respiratory manifestations (mainly asthma), 6/11 had cardiac disease, 6/11 had neurological symptoms, 7/11 had ENT manifestations, and 2 patients had cutaneous vasculitis (Table 2). Noteworthy, 3/6 patients with neurological manifestations had stroke, of cardioembolic origin in 2 cases.

Patients with heart disease related to EGPA had more than one type of cardiac involvement: atrial fibrillation in 2/11, pericarditis in 5/11, chronic heart failure in 3/11, cardiogenic shock requiring extracorporeal circulation (ECMO) [21] in one patient and STEMI-like myocardial

Table 1
Baseline characteristics of EGPA patients and healthy subjects (controls).

Baseline charateristics of EGPA patients and healthy subjects			
	EGPA	Healthy subjects	P-Value
N. patients	11	11	–
Age	50.5 ± 15	45 ± 10	0.67
Men/Women	6/11	7/11	1
Hemoglobin (g/dl)	13.47 ± 1.68	13.8 ± 0.7	0.397
Creatinine (mg/dl)	0.91 ± 0.32	0.85 ± 0.3	0.713
Urea (mg/dl)	39 ± 17	37 ± 13	0.493
Hematocrit (%)	40.3 ± 4.2	40.7 ± 3.0	0.453
Cardiovascular risk factors			
Hypetension	2	0	0.476
Dyslipidemia	0	0	1
Smoking	0	0	1
Diabetes	0	0	1