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Impact of systemic immune-mediated diseases on clinical features and prognosis of patients with biopsy-proved myocarditis

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ABSTRACT

Introduction: Myocarditis has been described in association with many systemic immune-mediated diseases (SIDs). However, the role of SIDs in influencing clinical presentation and outcome of patients with a new diagnosis of biopsy-proved myocarditis, has never been investigated so far.
Methods: We enrolled 25 consecutive cases with biopsy-proved myocarditis in the context of SIDs, and controls with isolated myocarditis, matched 1:1 by age, gender, ethnicity and clinical presentation. All of the patients presented with acute symptoms, normal coronary arteries, and no previous history of myocarditis. Detailed diagnostic workup, including blood exams, echocardiogram, arrhythmia monitoring and cardiac magnetic resonance (CMR) were obtained at baseline and at defined time points, up to 12-month follow-up (FU).
Results: At presentation, patients with SIDs had more commonly inflammatory biomarkers elevation, signs of associated pericarditis, and replacement fibrosis at histology, as compared to controls (18 vs. 6, 20 vs. 12, and 21 vs. 11, respectively; all $p < 0.05$). The Lake Louise criteria at CMR were negative in 19 vs. 10 patients with and without underlying SIDs, respectively ($p = 0.021$). Baseline ECG, in-hospital arrhythmia telemonitoring and echocardiographic findings were not significantly different between groups (all p = n.s.). At 12-month FU, the composite major endpoint of cardiac death, end-stage heart failure or malignant ventricular arrhythmias was significantly more common in cases than in controls (7 vs. 1, respectively, $p = 0.049$).
Conclusion: In patients with a new diagnosis of myocarditis, the presence of underlying SIDs is associated with distinct baseline clinical features and a significantly worse 1-year outcome.

1. Introduction

Myocarditis may occur either as an isolated heart disease, or as a component of systemic immune-mediated diseases (SIDs) [1]. Since cardiac involvement in SIDs can be extremely heterogeneous and often not limited to the myocardium, little is known, specifically, about baseline features and outcome of myocarditis in such a clinical setting [2]. In fact, cardiovascular research in this field is limited by several factors, applying to both SIDs (low prevalence, high inter-variability, poor cardiovascular profiling) and myocarditis (lack of universal definition, multiple clinical presentations, significant underdiagnosis) [2]. In particular, two key questions remain nowadays unsolved: 1) how do patients with their first diagnosis of myocarditis and underlying SIDs differ from those with isolated heart disease at presentation? 2) In the presence of biopsy-proved myocarditis and uniform clinical management, do SIDs significantly influence outcome? We present here a prospective study, aiming at evaluating the impact of SIDs on both clinical presentation and prognosis, in patients with their first diagnosis of biopsy-proved myocarditis and otherwise comparable baseline characteristics.

2. Methods

2.1. Study design

We screened, from January 2013 to June 2017, 156 consecutive patients presenting to a third-level hospital with acute symptoms and a final diagnosis of active myocarditis, defined by endomyocardial biopsy (EMB) according to standard criteria [1]. None of the

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patients had suspected or diagnosed previous myocarditis. Clinical presentation included acute coronary syndrome (ACS)-like, acute heart failure (AHF) and ventricular arrhythmias (VA). All of the patients underwent baseline evaluation consisting of detailed anamnestic questionnaire, complete blood exams (including T troponin = Tn T, with at least three samples per patient within 48 h; NT-proBNP; C-reactive protein = CRP; erythrocyte sedimentation rate = ESR), 12-leads ECG, continuous in-hospital ECG telemonitoring, transthoracic Doppler echocardiogram, and contrast-enhanced cardiac magnetic resonance (CMR). Furthermore, coronary angiography or CT scan was obtained in all of the patients, showing no significant abnormalities in epicardial coronary arteries. We enrolled consecutive cases ($n = 25$) with diagnosis of SIDs at baseline, according to accepted definition (group S) [2], and controls with lone myocarditis (group L). Controls ($n = 25$) were chosen based on 1:1 matching by age, gender, ethnicity and type of clinical presentation (ACS-like, AHF, or VA). Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Medical and device therapies were driven by the best clinical practice, integrating updated guidelines indications [1,3–6] with the experience of a third-level center. Immunosuppressive therapy (IST) was started or modified after consultation with an ad-hoc team of immunologists. Prospective follow-up (FU) was obtained at 3, 6 and 12 months with clinical evaluation, blood exams including blood biomarkers (Tn T, NT-proBNP, CRP, ESR), echocardiogram, 12-leads ECG, and 24-hour Holter ECG monitoring, together with device telemetric interrogation in implantable cardioverter defibrillator (ICD) carriers. Finally, 12-month FU CMR was obtained in all of the patients.

2.2. Endpoints

We considered the following single and composite major endpoints: cardiac death; end-stage HF (EHF), defined as worsening HF with accepted indication to heart transplantation; malignant VA (MVA), defined as either sustained ventricular tachycardia, ventricular fibrillation, or appropriate ICD intervention due to VA.

Among minor events, in addition to symptoms and NYHA class, we considered both the presence and timeline of any detectable abnormality at FU biomarkers, ECG, Holter ECG or ICD monitoring, echocardiogram, and CMR. Cutoff values for echocardiographic parameters were chosen based on updated references [7]. The Lake Louise criteria were analyzed at baseline CMR [8]. Normalization or improvement (defined as complete clearance of abnormal tissue signal in at least one segment) of T2-weighted/STIR and late gadolinium enhancement (LGE) sequences, were evaluated at FU CMR.

2.3. Statistical analysis

SPSS Version 20 (IBM Corp., Armonk, New York) was used for analysis and some of the graphic presentations, and Prism Version 6 (GraphPad Software Inc., La Jolla, California) was used for the remaining graphic presentations. Continuous variables were expressed as mean and standard deviation, or as median and IQR of 25th to 75 h percentiles, depending on the distribution of data. Accordingly, they were compared by parametric (Student T) or non-parametric (Mann-Whitney U) tests, respectively. Categorical variables were reported as counts and percentages, and were compared by using the Fisher exact test, where applicable. Clinical events were described both as raw number of events and percentages, and as cumulative event rates using the Kaplan-Meier method. Multivariable model with Cox regression analysis was used to identify independent predictors of the composite major endpoint by the end of FU. ROC statistics was used to retrospectively evaluate the accuracy of specific baseline features in identifying SIDs. Where relevant, 2-sided p-values < 0.05 were considered as statistically significant. Confidence intervals were set at 95%.

3. Results

3.1. Baseline evaluation

3.1.1. Clinical findings

Clinical information about SID types and group S patients are reported in Table 1. Median age at clinical onset was 43 (39–58) years, with 56% females and 84% Caucasians. Myocarditis presentation in each group was ACS-like ($n = 6$), AHF ($n = 6$), and VA ($n = 13$). As shown in Table 2, S and L groups did not differ in terms of cardiovascular risk profile, lifestyle, family history of cardiac or autoimmune diseases, and major comorbidities like chronic kidney disease, anemia and chronic obstructive pulmonary disease (all p = n.s.). A history of fever or infection in the 30 days preceding in-hospital admission were reported in 8 patients (4 S vs. 4 L, p = n.s.).

3.1.2. Laboratory findings

Overall, cardiac biomarkers (Tn T, NT-proBNP) were abnormal in 90% of patients (22 S vs. 23 L, p = n.s.), with higher NT-proBNP in group S (median 760 vs. 199 pg/mL, $p = 0.007$), and no significant differences in both baseline and peak Tn T values (p = n.s.). By converse, alterations in inflammatory indexes were significantly more common in group S (21 vs. 11 patients, $p = 0.007$). Concordantly with CRP and ESR values (median in S and L groups 7.6 vs. 1.4 mg/L, $p = 0.002$, and 14 vs. 5 mm/h, $p = 0.001$, respectively), both white blood cells and neutrophils were higher among patients with SIDs, as shown in Table 2.

Table 1
Information about patients with SIDs.
Complete data about group S baseline characteristics, type of SIDs, and major events during FU are reported in this table.
Abbreviations: ACS = acute coronary syndrome; AHF = acute heart failure; APLS = anti-phospholipid syndrome; ASS = anti-synthetase syndrome; DM = dermatomyositis; EGPA = eosinophilic granulomatosis with polyangiitis (Churg-Strauss disease); F = female; GCA = giant cell arteritis (Horton disease); GPA = granulomatosis with polyangiitis (Wegner's disease); GVHD = graft-versus-host disease; LVEF = left ventricular ejection fraction; M = male; MCTD = mixed connective tissue disease; MVA = malignant ventricular arrhythmias; PM = polymyositis; RA = rheumatoid arthritis; SCL = systemic sclerosis; SLE = systemic lupus erythematosus; VA = ventricular arrhythmias.

Patient N	Age	Gender	SIDS	Presentation	Baseline LVEF	Major events by 12 months
1	69	F	SCL	VA	25	0
2	49	M	Sarcoidosis	VA	41	MVA
3	46	M	Sarcoidosis	VA	60	0
4	44	F	RA	VA	54	0
5	35	F	MCTD	ACS-like	57	0
6	60	M	EGPA	ACS-like	60	0
7	41	F	MCTD	AHF	62	0
8	39	F	SLE, APLS	VA	57	0
9	42	M	SLE, APLS	VA	50	MVA
10	39	F	SLE	ACS-like	50	0
11	38	M	Sarcoidosis	VA	55	0
12	65	M	DM-ASS	VA	55	EHF, MVA, death
13	29	F	GPA	VA	61	MVA
14	79	F	EGPA	AHF	55	0
15	43	M	GVHD	ACS-like	56	MVA
16	40	F	SCL	AHF	56	0
17	54	F	PM	VA	56	0
18	43	F	SCL	AHF	20	0
19	37	F	GVHD	VA	55	EHF, death
20	43	F	MCTD	AHF	36	0
21	33	M	Sarcoidosis	VA	55	EHF, MVA, death
22	59	M	DM-ASS	ACS-like	60	0
23	54	M	PM	AHF	60	0
24	72	M	GCA	ACS-like	65	0
25	57	F	Sarcoidosis	VA	55	0

3.1.3. Histologic findings

The most common myocarditis histotype was lymphocytic in both groups. However, different inflammatory infiltrates were found in group S only (7 vs. 0, $p = 0.050$), including non-caseating granulomas ($n = 3$) and eosinophils ($n = 2$) in patients diagnosed with sarcoidosis and Churg-Strauss disease, respectively. Of note, EMB showed replacement fibrosis in the majority of group S patients (20/25 vs. 12/25 in group L, $p = 0.038$), involving a greater number of tissue samples (on average 1.6 vs. 1.0, respectively, $p = 0.039$). Furthermore, signs of coronary microvascular disease including microthrombi, perivascular inflammation and tunica media hypertrophy were found in 6 patients with SIDs but no one with lone myocarditis ($p = 0.022$). No differences between groups were detected in cardiac myocytes dimension (p = n.s.; complete information available in Table 2).

3.1.4. ECG and telemonitoring findings

Baseline ECG showed sinus rhythm in 19 group S vs. 20 group L patients (p = n.s.). The remaining subjects presented with a sustained VA. No significant differences between S and L groups were found in baseline ST-segment and T-wave abnormalities, as well as in PQ, QRS and QTc intervals (all p = n.s.). At continuous telemonitoring, the occurrence of paroxysmal atrial fibrillation and second- or third-degree atrioventricular block (AVB) was identical between groups (both p = n.s.). Before discharge, new VA episodes were detected in

Table 2
Baseline characteristics in S and L groups.
Complete clinical, laboratory, histologic, ECG, telemonitoring and imaging findings in S and L groups are shown in this table. Statistical significance of comparative tests is reported in the last column (*p*-value).
Abbreviations: ACS = acute coronary syndrome; AHF = acute heart failure; AVB = atrioventricular block; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CVRFs = cardiovascular risk factors; DVT-PE = deep vein thrombosis-pulmonary embolism; EGE = early gadolinium enhancement; ESR = erythrocyte sedimentation rate; IQR = interquartile range; LA = left atrium; LAV(i) = left atrial volume (index); LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; LVEDV(i) = left ventricular end-diastolic volume (index); NSVT = non-sustained ventricular tachycardia; PAD = peripheral artery disease; PAF = paroxysmal atrial fibrillation; PVCs = premature ventricular complexes; RV = right ventricle; RVEDD = right ventricular end-diastolic diameter (RV2); SD = standard deviation; STIR = short time inversion recovery sequences; TAPSE = tricuspid annular plane systolic excursion; Tn T = T troponin; VA = ventricular arrhythmias; VT = sustained ventricular tachycardia; WBC = white blood cells.

	Units	S ($N = 25$)	L ($N = 25$)	*p*-Value
Clinical features				
Presentation				
ACS-like	N	6	6	1.000
AHF	N	6	6	1.000
VA	N	13	13	1.000
Male gender	N	11	11	1.000
Age (years)	Median (IQR)	43 (39–58)	43 (39–58)	1.000
Caucasian ethnicity	N	21	21	1.000
Prodromic infection	N	4	4	1.000
Family history				
Sudden cardiac death	N	0	1	1.000
Coronary artery disease	N	2	1	1.000
Cardiomyopathy	N	1	1	1.000
Autoimmune disease	N	8	8	1.000
CVRFs				
Hypertension	N	10	4	0.114
Type-2 diabetes	N	0	1	1.000
Dyslipidemia	N	5	4	1.000
Cigarette smoke	N	4	1	0.349
Lifestyle				
Alcohol intake > 1 U daily	N	6	5	1.000
Drug abuse (former)	N	5	4	1.000
Comorbidities				
CKD	N	3	0	0.235
Anemia	N	4	3	1.000
COPD	N	0	0	1.000
Interstitial lung disease	N	4	1	0.349
PAD, DVT/PE	N	4	1	0.349
Allergy (any)	N	6	4	0.725
Depression - anxiety	N	5	8	0.520
Hypothyroidism	N	3	4	1.000
Gastritis - celiac disease	N	2	1	1.000
Neoplasia	N	2	2	1.000
Blood exams				
WBC ($10^3/mm^3$)	Mean ± SD	10.5 ± 4.4	7.7 ± 2.1	0.010
Neutrophils (%)	Mean ± SD	70.4 ± 1 8.5	60.6 ± 7.7	0.020
Tn T baseline (ng/L)	Median (IQR)	22.2 (7.2–118.1)	16.9 (7.0–33.6)	0.778
Tn T peak (ng/L)	Median (IQR)	37.3 (9.7–446.0)	18.0 (12.9–58.3)	0.357
NT-proBNP (pg/mL)	Median (IQR)	760 (308–1928)	199 (125–448)	0.007
CRP (mg/L)	Median (IQR)	7.6 (3.2–21.2)	1.4 (0.4–2.9)	0.002
ESR (mm/h)	Mean ± SD	14 (6–32)	5 (3–12)	0.001
Creatinine (mg/dL)	Mean ± SD	0.90 ± 0.44	0.79 ± 0.19	0.264
Histology				
Lymphocytic	N	20	25	0.05
Other histotypes	N	5	0	0.05
Acute myocarditis	N	5	12	0.072
Chronic myocarditis	N	20	13	0.072
Fibrosis	N	20	12	0.038
Samples with fibrosis (N/4)	Mean ± SD	1.6 ± 1.0	1.0 ± 1.0	0.039
Microvascular abnormalities	N	6	0	0.022
Hypertrophy	N	12	15	0.571
Myocytes length (μm)	Mean ± SD	16.7 ± 3.7	18.2 ± 5.7	0.292
12-leads ECG				
Sinus rhythms	N	19	20	1.000
Heart rate (bpm)	Mean ± SD	76 ± 17	74 ± 16	0.629
PQ (ms)	Mean ± SD	174 ± 30	161 ± 24	0.095
PQ > 200 ms	N	5	3	0.702
QRS (ms)	Mean ± SD	101 ± 26	98 ± 20	0.611
QRS > 120 ms	N	7	4	0.496
QTc	Mean ± SD	425 ± 30	419 ± 28	0.259
ST-segment abnormalities	N	5	5	1.000
T-wave abnormalities	N	16	13	0.567
In-hospital telemonitoring				
2nd/3rd-degree AVB	N	3	3	1.000
PAF	N	3	3	1.000
PVCs/24 h	Median (IQR)	9 (0–180)	0 (363)	0.277
NSVT	N	2	4	0.667
VT	N	1	1	1.000
Transthoracic Doppler echocardiogram				
LVEDVi (mL/m^2)	Mean ± SD	56.2 ± 11.2	58.3 ± 18.1	0.633
LV dilatation	N	5	6	1.000
LVEF (%)	Mean ± SD	52.6 ± 11.0	50.6 ± 13.3	0.558
LVEF < 40%	N	3	4	1.000
LAVi (mL/m^2)	Mean ± SD	27.0 ± 8.7	28.7 ± 12.6	0.577
LA dilatation	N	5	8	0.520
E/E′	Mean ± SD	8.1 ± 3.3	8.5 ± 4.2	0.699
Diastolic dysfunction	N	12	10	0.776
RVEDD (mm)	Mean ± SD	29.8 ± 5.7	31.6 ± 6.4	0.278
RV dilatation	N	2	4	0.667
TAPSE (mm)	Mean ± SD	21.8 ± 4.3	21.0 ± 2.9	0.440
RV dysfunction	N	4	5	1.000
Pulmonary hypertension	N	3	4	1.000
Valvular regurgitation > 2+	N	0	0	1.000
Cardiac magnetic resonance				
Positive Lake Louise criteria	N	6	15	0.021
LGE positivity	N	21	21	1.000
Number LV segments (N/17)	Mean ± SD	4.8 ± 3.0	4.0 ± 3.4	0.341
Number LV wall layers (N/3)	Mean ± SD	1.3 ± 0.9	1.2 ± 0.7	0.483
RV involvement	N	4	2	0.667
STIR positivity	N	8	16	0.046
EGE positivity	N	2	3	1.000
LGE+ STIR−	N	13	5	0.0378
Pericarditis	N	18	6	0.002

3 S vs. 5 L patients, with a comparable median number of premature ventricular complexes (PVCs)/24 h per patient (both p = n.s.). Complete data about baseline ECG and in-hospital telemonitoring are shown in Table 2.

3.1.5. Imaging findings

At first echocardiogram, S and L patients presented with comparable left ventricular end-diastolic volume (LVEDV) and ejection fraction (LVEF) values (mean LVEDVi 56.2 vs. 58.3 mL/m^2, mean LVEF 52.6 vs. 50.6%, respectively, both p = n.s.). Furthermore, as shown in Table 2, no significant differences between groups were found in diastolic dysfunction, left atrium dimension, right ventricular dilatation or dysfunction, pulmonary hypertension or relevant valve diseases (all p = n.s.). At CMR, non-ischemic LGE was documented in 21 patients in each group (p = n.s.), with a comparable number of segments and wall

Table 3
Follow-up endpoints in S and L groups.
Complete clinical, laboratory, ECG, telemonitoring and imaging findings in S and L groups at each FU time point (3, 6, 12 months) are reported in this table. Statistical significance of comparative tests is reported in the last column (*p*-value).
Abbreviations: AVB = atrioventricular block; CKD = chronic kidney disease; CRP = C-reactive protein; CVRFs = cardiovascular risk factors; EHF = end-stage heart failure; ESR = erythrocyte sedimentation rate; IQR = interquartile range; LA = left atrium; LAV(i) = left atrial volume (index); LGE = late gadolinium enhancement; LV = left ventricle; LVEF = left ventricular ejection fraction; LVEDV(i) = left ventricular end-diastolic volume (index); MVA = malignant ventricular arrhythmias; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association; PAF = paroxysmal atrial fibrillation; PVCs = premature ventricular complexes; RV = right ventricle; RVEDD = right ventricular end-diastolic diameter (RV2); SD = standard deviation; STIR = short time inversion recovery sequences; TAPSE = tricuspid annular plane systolic excursion; Tn T = T troponin; VA = ventricular arrhythmias; VT = sustained ventricular tachycardia; WBC = white blood cells.

	Units	FU (month)	S ($N = 25$)	L ($N = 25$)	*p*-Value
Major endpoints					
Cardiac death	N	3	1	0	1.000
	N	6	1	0	1.000
	N	12	3	0	0.235
EHF	N	3	1	0	1.000
	N	6	1	0	1.000
	N	12	3	0	0.235
MVA	N	3	2	1	1.000
	N	6	3	1	0.609
	N	12	6	1	0.098
Composite major endpoint	N	3	3	1	0.609
	N	6	3	1	0.609
	N	12	7	1	0.049
Symptoms					
Symptoms	N	3	19	21	0.725
	N	6	14	18	0.377
	N	12	11	14	0.572
NYHA class III–IV	N	3	2	2	1.000
	N	6	3	1	0.609
	N	12	3	1	0.609
Blood exams					
TnT (ng/L)	Mean ± SD	3	25.6 (4.5–44.3)	7.7 (3.3–14.7)	0.106
	Mean ± SD	6	14.5 (5.4–27.0)	4.0 (3.0–5.1)	<0.001
	Mean ± SD	12	7.4 (3.0–13.0)	3.0 (3.0–4.0)	0.029
NT-proBNP (pg/mL)	Mean ± SD	3	327 (84–3212)	123 (107–255)	0.125
	Mean ± SD	6	170 (65–1815)	110 (85–243)	0.327
	Mean ± SD	12	105 (37–572)	109 (64–141)	0.915
CRP (mg/L)	Mean ± SD	3	3.3 (1.7–7.8)	1.5 (1.0–4.0)	0.065
	Mean ± SD	6	4.2 (1.6–14.8)	1.1 (0.7–2.0)	0.002
	Mean ± SD	12	3.4 (1.0–5.9)	1.1 (0.7–2.0)	0.021
ESR (mm/h)	Mean ± SD	3	9 (6–13)	3 (2–6)	<0.0001
	Mean ± SD	6	8 (6–13)	3 (1–5)	<0.0001
	Mean ± SD	12	7 (4–12)	3 (2–4)	0.004
12-leads ECG					
PQ (ms)	Mean ± SD	3	178 ± 35	161 ± 26	0.088
	Mean ± SD	6	180 ± 41	161 ± 29	0.069
	Mean ± SD	12	185 ± 47	163 ± 33	0.056
QRS (ms)	Mean ± SD	3	102 ± 27	98 ± 21	0.548
	Mean ± SD	6	105 ± 29	100 ± 20	0.337
	Mean ± SD	12	109 ± 29	100 ± 20	0.239
QRS > 120 ms	N	3	0	1	1.000
	N	6	2	1	1.000
	N	12	3	1	0.609
QTc	Mean ± SD	3	426 ± 30	420 ± 25	0.264
	Mean ± SD	6	427 ± 33	422 ± 29	0.488
	Mean ± SD	12	425 ± 28	419 ± 23	0.221
ST-segment abnormalities	N	3	0	0	1.000
	N	6	1	0	1.000
	N	12	3	0	0.235
T-wave abnormalities	N	3	1	1	1.000
	N	6	3	2	1.000
	N	12	5	4	1.000
24 h Holter ECGs and (when applicable) device interrogation					
Pauses > 3 s	N	3	0	0	1.000
	N	6	1	0	1.000
	N	12	2	1	1.000
1st-degree AVB	N	3	2	0	0.490
	N	6	2	0	0.490
	N	12	4	0	0.110
2nd-degree AVB	N	3	1	0	1.000
	N	6	2	0	0.490
	N	12	3	1	0.609
3rd-degree AVB	N	3	0	0	1.000
	N	6	1	0	1.000
	N	12	1	0	1.000
Atrial tachycardia	N	3	1	2	1.000
	N	6	1	2	1.000
	N	12	2	2	1.000
PAF	N	3	0	0	1.000
	N	6	0	1	1.000
	N	12	2	2	1.000
PVCs > 1000/24 h	N	3	0	0	1.000
	N	6	0	0	1.000
	N	12	0	1	1.000
NSVT	N	3	2	0	0.490
	N	6	2	1	1.000
	N	12	2	1	1.000
VT	N	3	1	0	1.000
	N	6	1	0	1.000
	N	12	4	0	0.110
Transthoracic Doppler echocardiogram					
LVEDVi (mL/m^2)	Mean ± SD	3	56.1 ± 16.8	58.6 ± 19.4	0.591
	Mean ± SD	6	59.7 ± 19.2	57.1 ± 21.8	0.607
	Mean ± SD	12	61.1 ± 26.2	56.9 ± 26.9	0.316
New LV dilatation	N	3	3	0	0.235
	N	6	8	4	0.321
	N	12	8	6	0.754
LVEF (%)	Mean ± SD	3	49.8 ± 14.0	52.1 ± 11.6	0.534
	Mean ± SD	6	47.7 ± 14.8	54.2 ± 10.3	0.079
	Mean ± SD	12	45.8 ± 20.2	54.3 ± 10.5	0.071
New LVEF < 40%	N	3	4	2	0.667
	N	6	6	2	0.247
	N	12	6	2	0.247
E/E′	Mean ± SD	3	8.3 ± 3.5	8.2 ± 3.8	0.896
	Mean ± SD	6	8.5 ± 4.1	7.5 ± 3.3	0.605
	Mean ± SD	12	8.8 ± 5.2	7.3 ± 2.7	0.206
New diastolic dysfunction > grade 1	N	3	1	0	1.000
	N	6	2	0	0.490
	N	12	4	0	0.110
LAVi (mL/m^2)	Mean ± SD	3	27.4 ± 8.2	29.2 ± 11.9	0.506
	Mean ± SD	6	28.1 ± 8.0	29.9 ± 12.1	0.516
	Mean ± SD	12	28.5 ± 7.8	30.6 ± 11.7	0.456
New LA dilatation	N	3	0	0	1.000
	N	6	1	0	1.000
	N	12	1	1	1.000
RVEDD (mm)	Mean ± SD	3	30.1 ± 6.0	31.5 ± 6.5	0.387
	Mean ± SD	6	30.8 ± 6.6	31.2 ± 6.7	0.608
	Mean ± SD	12	31.6 ± 7.3	31.6 ± 6.6	1.000
New RV dilatation	N	3	2	0	0.490
	N	6	4	0	0.110
	N	12	4	1	0.349
TAPSE (mm)	Mean ± SD	3	21.8 ± 4.3	21.2 ± 2.4	0.748
	Mean ± SD	6	20.6 ± 5.5	21.9 ± 4.1	0.231
	Mean ± SD	12	19.9 ± 6.0	21.8 ± 3.3	0.177
New RV dysfunction	N	3	2	0	0.490
	N	6	3	1	0.609
	N	1212	4	4	1.000
New pulmonary hypertension	N	3	2	0	0.490
	N	6	4	0	0.110
	N	12	5	1	0.190
Valvular regurgitation > 2+	N	3	0	0	1.000
	N	6	1	1	1.000
	N	12	2	1	1.000
Cardiac magnetic resonance (device carriers excluded, N = 8 in each group)					
STIR improvement	N	12	2/8	10/13	0.032
STIR normalization	N	12	1/8	8/13	0.067

Table 3 (*continued*)

	Units	FU (month)	S ($N = 25$)	L ($N = 25$)	*p*-Value
LGE improvement	N	12	0/17	7/17	0.007
LGE normalization	N	12	0/17	4/17	0.103

layers involved (both p = n.s.). However, T2-weighted/STIR sequences showed abnormalities in 8 S vs. 16 L patients ($p = 0.046$), and the Lake Louise criteria were positive in 6 vs. 15 cases, respectively ($p = 0.021$). Significantly, 18 patients with SIDs vs. 6 with isolated myocarditis had imaging signs of pericardial inflammatory involvement ($p = 0.002$).

3.1.6. Treatment

Acute-phase treatment included inotropes or mechanical circulatory support in 2 patients with fulminant presentation (1 S and 1 L, p = n.s.). Furthermore, 16 patients (8 vs. 8, p = n.s.) underwent ICD implantation: the most common indication was secondary prevention (7 S and 6 L, p = n.s.) in patients with in-hospital recurrences of MVA. Medical treatment at discharge was similar between groups (all p = n.s.), including betablockers (84% vs. 92%), ACE-inhibitors (60% vs. 68%), diuretics (52% vs. 48%) and anti-arrhythmic drugs (28% vs. 28%), with no significant changes in FU. Following myocarditis diagnosis, 12 of the 22 group S patients underwent IST modification, while 10 patients with isolated heart disease started a de novo IST (p = n.s.).

3.2. Follow-up

3.2.1. Major endpoints

Overall, major events in FU occurred more frequently in patients with SIDs than in those with isolated myocarditis: cardiac death (3 vs. 0), EHF (3 vs. 0), and MVA (6 vs. 1), respectively (p for composite major endpoint = 0.049). The causes of death were EHF ($n = 2$) and electrical storm ($n = 1$). Of note, because of sudden clinical worsening, none of the patients underwent heart transplantation.

In particular, as shown in Table 1, an adverse outcome was found in patients with chronic graft-versus-host disease ($n = 2/2$), sarcoidosis ($n = 2/5$), granulomatosis with polyangiitis ($n = 1/1$), systemic lupus erythematosus with anti-phospholipid syndrome ($n = 1/2$), and dermatomyositis with anti-synthetase syndrome ($n = 1/2$). By converse, no events occurred among patients with mixed connective tissue disease (0/3), Churg-Strauss syndrome (0/2), polymyositis (0/2), systemic sclerosis (0/2), rheumatoid arthritis (0/1) and giant cell arteritis (0/1).

At multivariable analysis, no independent predictors for the composite major endpoint were found, including: chronic kidney disease, diabetes, baseline elevation in cardiac or inflammatory biomarkers, left or right ventricular dilatation or dysfunction at presentation, associated pericarditis, in-hospital recurrences of VA or second/third-degree AVB, LGE extension, and replacement fibrosis at histology (all p = n.s.).

3.2.2. Minor endpoints

Data about FU minor events and their timeline are reported in Table 3 and Fig. 1, respectively. Symptoms and ECG findings during FU were comparable between groups (all p = n.s.). By converse, patients

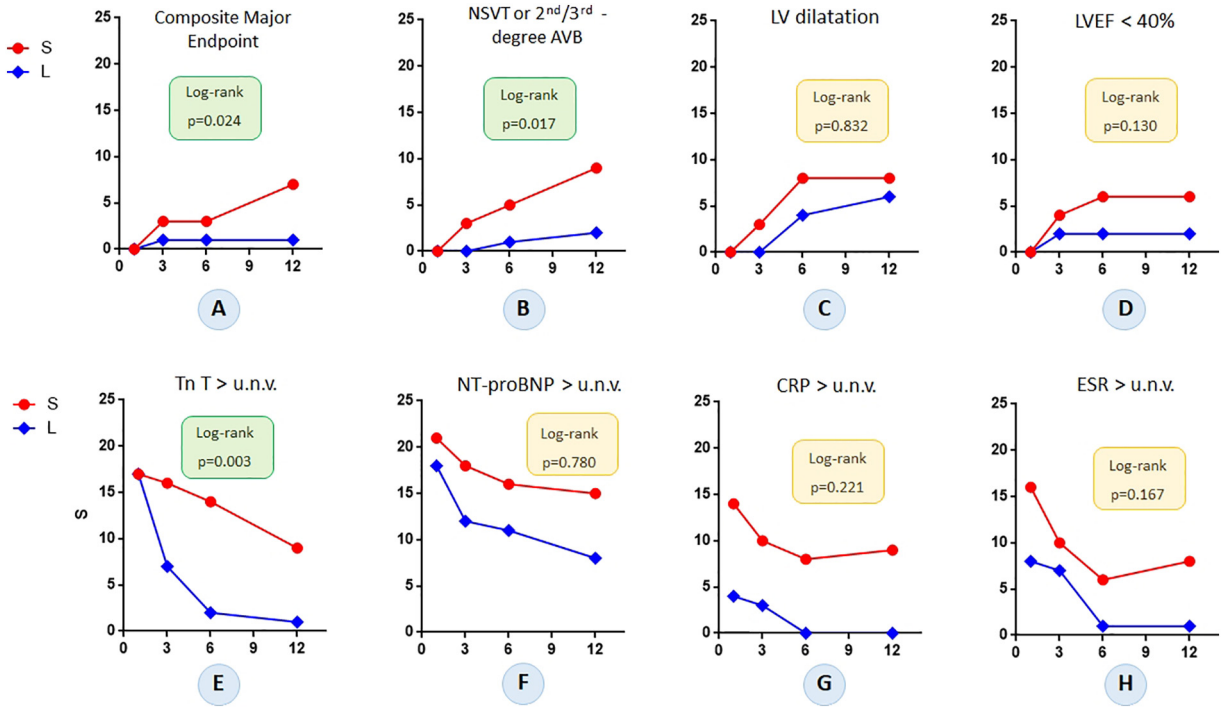

Fig. 1. Comparison of endpoint timelines in groups. Timelines for the main study endpoints in each group are represented in this figure. In each plot (A-H), red curves refer to group S, and blue curves to group L. X-axis shows FU timeline in months. Y-axis shows the cumulative number of patients reaching the endpoint. The first-line plots (A–D) show significantly different curves for the major endpoint of the study (cardiac death, EHF, MVA) and for the composite endpoint of NSVT or 2nd/3rd degree AVB (Log-rank $p = 0.0024$ and 0.0017, respectively), both occurring more commonly in group S. By converse, no significant differences between groups are seen in de novo occurrence of LV dilation or systolic dysfunction with a LVEF cutoff of 40% (Log-rank p = n.s.). As for blood biomarkers abnormalities (plots E–H), significantly different curves between S and L groups are found only for Tn T (Log-rank $p = 0.003$), showing a greater and faster trend towards normalization among patients with isolated myocarditis. Of note, in spite of no significant differences between curves (Log-rank p = n.s.), only in group L inflammatory indexes (CRP, ESR) show an almost complete normalization within 6 months, persisting even at 12 months. Abbreviations: AVB = atrioventricular block; CRP = C-reactive protein; DCM = dilated cardiomyopathy; EHF = end-stage heart failure; ESR = erythrocyte sedimentation rate; LVEF = left ventricular ejection fraction; MVA = malignant ventricular arrhythmias; NSVT = nonsustained ventricular tachycardia; Tn T = T troponin; u.n.v. = upper normal reference value.

with SIDs had significantly higher CRP, ESR, and Tn T values at 6 and 12 months (all $p < 0.05$). In particular, only patients with isolated myocarditis had normalization of inflammatory indexes by 6 months, persisting even at 12 months. Holter ECGs and ICD telemonitoring documented a higher occurrence of arrhythmias in group S (9 vs. 2, considering nonsustained VA and second/third-degree AVB, $p = 0.037$), with no differences in supraventricular arrhythmias (p = n.s.). Even in the absence of statistical significance, new structural or functional echocardiographic abnormalities were more commonly found among SIDs patients, as shown in Table 3 and Fig. 1. Finally, although 12-month FU CMR was performed in 100% of the patients, because of significant ICD-related artifacts, reliable data were obtained in non-device carriers only ($n = 17$ in each group): of them, signs of improvement at T2-weighted/STIR and LGE sequences were less commonly observed in patients with SIDs (respectively: 0/17 S vs. 2/8 L, $p = 0.032$; and 7/17 S vs. 10/13 L, $p = 0.007$).

3.2.3. Retrospective identification of SIDs

In our study, 3 group S patients were diagnosed with both SIDs and myocarditis during the index hospitalization. Given the higher occurrence of both major and minor events in group S, we estimated that early identification of possible underlying SIDs, may be an extremely useful clinical issue in patients with a new diagnosis of myocarditis. Thus, through a retrospective analysis, we found that the presence of at least two of the following baseline characteristics was significantly associated with known or unknown underlying SIDs (sensitivity 76%, specificity 84%, positive predictive value 81%, negative predictive value 72%, ROC-curve AUC 0.76, $p < 0.0001$): 1) abnormalities in inflammatory indexes (CRP and/or ESR); 2) imaging signs of associated pericarditis; 3) replacement fibrosis at histology. Of note, the presence or absence of all of the 3 features above, allowed, respectively, for the best SIDs rule in (positive predictive value 100%, $p = 0.002$) and rule out (negative predictive value 100%, $p = 0.022$).

4. Discussion

We presented a single-center prospective study, comparing baseline characteristics and outcome of patients with myocarditis, in the presence or absence of underlying SIDs.

It should be noted that all of the patients had an EMB-proved diagnosis of myocarditis, as universally accepted [1,2], and that potentially confounding factors (like age, gender, and clinical presentation) have been eliminated by the study design; furthermore, comorbidities and treatment were not significantly different between groups.

We found remarkable differences in baseline characteristics of patients with and without SIDs. In particular, irrespective of SID type, group S patients with myocarditis had more commonly: 1) abnormalities in inflammatory indexes; 2) imaging signs of associated pericarditis; 3) replacement fibrosis at histology. By converse, baseline ECG, telemonitoring and functional echocardiographic findings did not help significantly in differentiating groups.

As for CMR, we showed that the Lake Louise criteria were negative in the majority of group S patients with a biopsy-proved myocarditis. Our results are consistent with a very recent paper, pointing at the limitations of the Lake Louise criteria in patients with SIDs [9]. At the same time, our findings enforce the evidence that EMB is still the cornerstone for myocarditis diagnosis in patients with SIDs [1,2]. Consistently with the histological findings of replacement fibrosis, however, the proportion of patients with "STIR negative, LGE positive" CMR was significantly higher in group S; in addition, none of the patients with SIDs showed LGE modification at FU CMR. These findings call for the necessity of improving noninvasive evaluation of chronic inflammation, in particular in patients with SIDs and virtually silent myocarditis: new insights from the modern T1 and T2 mapping techniques and from CMR-PET fusion imaging may be extremely useful in this context [10].

During FU, major events occurred more frequently among patients with SIDs. Of note, in our study prognosis was not significantly influenced by non-lymphocytic histotypes or VA at presentation. In fact: a) only 2/5 patients with granulomatous or eosinophilic myocarditis, underwent adverse outcome by 12 months, with the majority of events ($n = 5$) occurring in lymphocytic myocarditis cases; b) although 7/7 group S patients undergone major events had VA at presentation, FU was uneventful in 13/14 group L patients with an identical arrhythmic presentation.

Moreover, in spite of medical treatment, patients with SIDs underwent a greater amount of minor events too, including persistent biomarkers alteration, relevant arrhythmias and echocardiographic abnormalities. All of these findings suggest the necessity of a strict and careful cardiological FU, in all of the patients diagnosed with myocarditis in the context of SIDs. Furthermore, they support the usefulness of EMB to early diagnose and treat patients with heart involvement in SIDs, as already demonstrated in systemic sclerosis [11,12].

Finally, from the combination of baseline features (i.e. abnormal inflammatory indexes, associated pericarditis, replacement fibrosis), we proposed a possible method for identifying SIDs, in patients with a new diagnosis of myocarditis. However, given the small sample size, these findings need to be confirmed by larger studies in the future, in order to personalize patients FU and treatment, based on early identification of underlying SIDs.

4.1. Limitations

Some limitations should be considered in our study. First of all, many types of SIDs have been included within the same group: as a consequence, results generalization can be limited by disease-specific clinical and prognostic features. However, the aim of the study was to describe simple but clinically useful baseline and FU findings, applicable to most of the SIDs. Second, as compared to AHF and ACS-like presentations, the proportion of patients presenting with VA was particularly elevated in our study, as a possible result of a referral bias. Importantly, PET scan and modern CMR techniques like T1 and T2 mapping, potentially more sensitive in detecting extracellular volume alterations and minimal signs of myocarditis, have not been used in this study. In parallel, potential limitations of EMB, such as invasiveness and possibility of sampling error, should be acknowledged. Finally, sample size and FU are limited to 50 patients and 12 months, respectively: larger prospective studies with a longer FU are required to validate or disconfirm our results, even focusing on specific SIDs.

5. Conclusion

Our study suggests that, in patients with EMB-proved myocarditis, the presence of an underlying SID is associated with peculiar clinical features at presentation, including abnormalities in inflammatory indexes, imaging signs of associated pericarditis and replacement fibrosis at histology. Although invasive and potentially affected by sampling errors, EMB is still a very useful diagnostic technique in patients with SIDs, since the Lake Louise criteria at CMR are often unmet in in this clinical setting. Importantly, patients with SIDs are at higher risk of 1-year adverse outcome, as compared to those with isolated myocarditis. Given their considerable impact on prognosis, early identification of underlying SIDs is a relevant issue in patients with a de novo diagnosis of myocarditis.

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Disclosures/conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.104.

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