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End-Stage Heart Failure in Cardiac Sarcoidosis

Short title: Cardiac Sarcoidosis

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Cardiac sarcoidosis (CS) is an inflammatory cardiomyopathy notorious for causing heart block and fatal ventricular arrhythmias in middle-aged individuals.[1] Manifest heart failure (HF) is not uncommon either, and extensive granulomatous involvement can eventuate in end-stage HF (ESHF) and death without transplantation or mechanical support.[1] The incidence and predictors of ESHF in CS remain poorly described.

We analyzed 512 cases of clinically manifest and biopsy-proven CS[4] included in the nationwide registry of Myocardial Inflammatory Diseases in Finland (MIDFIN)[2,3] from the late 1980s to the end of 2019. The MIDFIN database[2,3] included information on patients' demographics, clinical cardiac manifestations, diagnostic imaging, laboratory studies, and details of treatment and adverse events. We analyzed the time from presentation of CS to ESHF, wherein presentation was the first medical contact due to manifestations of CS and ESHF was specified as either referral for heart transplantation or death from HF. The causes of death were ascertained from clinical and autopsy reports. The patients were followed for all events till the end of 2020. The MIDFIN registry study was approved by the national ethical review board in 2009 (STM/1219/2009). Written informed consent was obtained from patients alive at the time of recruitment.

Cause-specific cumulative incidence analysis was used to construct time-to-ESHF curves and to calculate incidence estimates; the Gray test was used for group comparisons. Non-cardiac and sudden cardiac deaths were considered competing events. Factors predictive of ESHF were analyzed by uni- and multivariable Fine and Gray models[5] yielding subdistribution hazard ratios (SHR) with 95% confidence intervals (CI). Summary data are given as medians (interquartile range) or frequencies. P-values < 0.05 were considered statistically significant. Analyses were performed using the SPSS v.25.0 (IBM Corporation, USA) and R (version 4.0.4, R Foundation, Vienna, Austria.

At CS presentation, the patients´ median age was 52 years (43-58), and 70% of them (356/512) were women. The main presenting manifestation was atrioventricular block in 267 patients (52%), sustained ventricular tachycardia in 90 patients (18%), and congestive HF in 82 patients (16%); the rest 73 (14%) presented with premature beats or symptoms like chest pain, syncope, and dyspnea. The median presenting left ventricular ejection fraction (LVEF) was 55% (45-60%). Elevated cardiac troponins (exceeding the contemporaneous reference range) were found in 52% of patients (243/471), and 55% (228/417) had elevated natriuretic peptides (brain natriuretic peptide >100 ng/L or N-terminal brain natriuretic pro-peptide >400 ng/L). On positron emission tomography (n=133), 92% of patients had abnormal cardiac 18F-fluorodeoxyglucose uptake. Cardiac magnetic resonance imaging (CMRI, n=220) revealed late gadolinium enhancement (LGE) in 97% of patients; the medians of LVEF, right ventricular EF, and LGE mass were 49% (40-58%), 54% (46-61%), and 14% (8-22%), respectively. Treatment-wise, 501 patients (98%) received immunosuppression, 391 patients (76%) underwent implantation of a cardioverter-defibrillator, and 130 (25%) received a cardiac resynchronization therapy device.

Over median follow-up of 6.1 years (3.7-9.5 years), 6 patients died of terminal HF and 31 were referred for transplantation, while 26 suffered a competing death. Of patients referred for transplantation, 21 underwent transplant surgery and 2 died on the waiting list. The non-listed patients either had absolute contraindications (n=2), received an LV assist device (n=2), died during the evaluation process (n=2), or awaited its completion at the closure of our study (n=2). **Figure 1A** shows the time-to-ESHF graph with calculated incidence estimates. Univariable predictors of ESHF included HF as the presenting manifestation with a SHR of 2.66 vs other forms of presentation (1.25-5.65, p=0.011), LVEF with a SHR of 0.58 per +10% (0.45-0.76, p<0.001), elevated cardiac troponins with a SHR 3.59 (1.61-8.00, p=0.002), and elevated natriuretic peptides (see above) with a SHR of 4.64 (1.37-15.70, p=0.014). **Figures 1B-D**

compare the incidence graphs across patients stratified by presenting LVEF, cardiac troponins, and natriuretic peptides. Of the CMRI variables, LGE mass (n=198) predicted ESHF with a SHR of 1.44 per +5% (1.01-2.05, p=0.044) and RVEF (n=209) with a SHR of 0.47 per +10% (0.24-0.93, p=0.029). In multivariable analysis, the key independent predictors were echocardiographic LVEF with a SHR 0.66 per +10% (0.48-0.90, p=0.009) and elevation of cardiac troponins with a SHR 2.89 (1.24-6.74, p=0.014). Their predictive capacity was additive in that the 15-year incidence of ESHF was 25% (9-41%) in patients presenting with both elevated troponins and LVEF ≤50% (n=130, 18 ESHF events) but only 2% (0-7%) in those with EF >50% and non-elevated troponins (n=162, 3 ESHF events).

We found that 14 % of patients with clinically manifest CS lapsed into terminal HF within 15 years from disease presentation despite contemporaneous standard care. The risk of ESHF was associated with manifest HF at presentation and with laboratory and imaging biomarkers of the extent of myocardial involvement. Importantly, having both LVEF ≤50% and elevated cardiac troponins at presentation predicted a 1 in 4 risk of ESHF in the long run while the risk was only 1 in 50 in their absence.

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Disclosures

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Legend for figure 1.

Figure 1. Incidence graphs for end-stage heart failure (ESHF) in a 30-year Finnish cohort of biopsy-proven, clinically manifest cardiac sarcoidosis. Panel **1A** represents the cumulative incidence in the entire group of 512 patients while the other panels compare the respective graphs across the subgroups of CS stratified by presenting echocardiographic left ventricular ejection fraction (LVEF) (**1B**), elevation of cardiac troponins >reference range (**1C**), and elevation of either brain natriuretic peptide (BNP) >100 ng/L or N-terminal natriuretic propeptide (NT-proBNP) >400 ng/L (**1D**). ESHF was defined as referral for heart transplantation or death from terminal HF. Group comparisons were made using the Grey test. Shaded areas represent 95% confidence intervals.