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Discordant cardiac inflammation between ^{18}F-FDG PET and CMR in patients with cardiac sarcoidosis

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Abstract

Current diagnostic criteria for cardiac sarcoidosis (CS) rely on non-invasive imaging tools including positron emission tomography (PET-CT) and cardiac magnetic resonance (CMR). The aim of this study was to assess the prevalence of discordant myocardial inflammation between PET-CT and CMR in patients with known cardiac sarcoidosis. We retrospectively identified patients with both ^{18}F-FDG PET-CT and CMR who had histology-proven sarcoidosis (N=148). Among these 25 (17%) had abnormal ^{18}F-FDG metabolism with normal tissue characterization by CMR. Of these, 13 (9%) had the studies concomitantly within 180 days (median 5 days, IQR 1–31). During median follow up of 7 years, 3 (23%) deaths were documented. Although prospective studies are required to address the best imaging approach for cardiac inflammation, our observation that some patients with CS have evidence of disease activity on PET-CT, but not on limited CMR without mapping suggests that a negative limited CMR may not fully exclude CS.

The diagnosis of cardiac sarcoidosis (CS) is challenging due to patchy and heterogenous myocardial involvement which results in a low yield of detection on endomyocardial biopsy. Accordingly, current diagnostic criteria for CS by the Japanese Circulation Society, the World Association for Sarcoidosis and Other Granulomatous Disorders, and the Heart Rhythm Society (HRS) rely on non-invasive tools for diagnosis and management including positron emission tomography with computed tomography (PET-CT) and cardiac magnetic resonance imaging (CMR) (Birnie et al. 2014; Terasaki et al. 2019). Although these imaging techniques are complementary and often selected based on local imaging expertise, the ideal approach for diagnosis and disease monitoring in CS is not yet determined. (Coulden et al. 2020) The aim of the current study is therefore to assess the prevalence of discordant findings in the assessment of myocardial inflammation in patients with known cardiac sarcoidosis who undergo concomitant PET-CT and CMR, defined as abnormal (fluorine-18 fluorodeoxyglucose) ^{18}F-FDG metabolism by PET-CT with normal tissue characterization by CMR (absence of late gadolinium enhancement or edema on T2-weighted imaging).

A total of 2,358 patients with systemic sarcoidosis or suspected cardiac sarcoidosis who underwent CMR or PET-CT with sarcoidosis protocol between April 2001 and February 2021 were identified. Of these, 444 (19%) subjects had abnormal imaging findings suspicious for CS and 273 (12%) patients had definite CS by HRS criteria (histology-proven sarcoidosis). Among this group, 148 had both PET-CT and CMR, and these patients were included in the final cohort.

Myocardial perfusion imaging (MPI) to assess for mismatch in perfusion and metabolism was done using ^{82}Rb PET-CT. Patients were prepared for ^{18}F-FDG PET-CT with dietary modification using a high-fat, low-carbohydrate diet 24 hours prior to the test followed by at least 12 hours of fasting. CMR imaging was performed as per local protocol according to standards of practice at the time of the procedure. All CMRs included late gadolinium enhancement imaging and T2-weighted imaging using T2 Short Tau Inversion Recovery (T2 STIR). T1 mapping was obtained in more contemporary studies (after 2013). T2 mapping was obtained in a case-by-case basis. The institutional review board approved this retrospective study and the requirement to obtain informed consent was waived.

Overall, 25 (17%) patients had evidence of abnormal ^{18}F-FDG uptake by PET-CT but no late gadolinium enhancement (LGE) or evidence of myocardial edema on T2-weighted imaging (T2 STIR or T2 mapping). Of these 25 patients, we identified 13 (9%) who had concomitant PET-CT and CMR within 180 days (median 5 days, IQR 1–31) (Table 1).

The median biopsy to imaging time was 150 days (IQR 30-1460). A total of 2 patients had T2 mapping (both suboptimal quality), 6 had T1 mapping and 5 had no mapping performed. All patients received immunosuppressive therapy during the follow-up period, 92% (N=12) with prednisone, 69% (N=9) with methotrexate and 38% (N=5) with leflunomide. Figure 1 illustrates two cases with discordant tissue findings by PET-CT and CMR.

Median follow up was 7 years (IQR 4–10). During follow-up, there were no documented ventricular arrhythmia events or implantable cardiac defibrillator shocks. A total of 3 (23%) deaths were documented, 1 cardiac death related to end-stage cardiomyopathy and 2 non-cardiac related deaths. Furthermore, 5 patients had follow-up imaging, 2 with PET-CT only, 2 with PET-CT and CMR and 1 with CMR only. Among the 3 patients who had follow up CMR, 1 converted to positive LGE and 2 remained normal. Among those with follow up PET (N=4), all except 1 had resolution of myocardial ^{18}F-FDG uptake.

A total of 51 patients of 148 (34%) who had both PET-CT and CMR were documented to have concordant inflammation by PET-CT and abnormal tissue characterization by CMR. Of these 51, 27 (18%) had studies done within 180 days (median 19 days, IQR 0–44). Median follow up of these patients was 8 years (IQR 2–16). During follow up, 9 (33%) patients had ventricular arrhythmia and 7 (26%) had appropriate ICD therapy. A total of 5 deaths occurred (3 cardiac and 2 non-cardiac) and 1 patient underwent heart transplantation. All except one were treated with immunosuppressive therapy on follow up (96% with prednisone, 70% with methotrexate and 19% with leflunomide). The overall combined rate of ventricular arrhythmia and overall mortality was 52% (N=14) for patients with concordant positive PET-CT and CMR as compared to 23% (N=3) in

Table 1 Baseline characteristics of study population

Case	Age	Sex	Race	Presentation	PPM/ICD	LVEF PET/CMR (%)	^{18}F-FDG LV site	^{18}F-FDG pattern	SUV max	Mismatch PM	RV ^{18}F-FDG uptake	Extracardiac ^{18}F-FDG uptake	Biopsy site
1	64	M	Black	Heart failure	No/No	43/47	Basal to mid S	Focal	3.1	Yes	Yes	Mediastinal LN	Endomyocardial
2	65	M	White	Persistent AF	No/No	59/61	Basal to mid AS, AL	Focal	4.2	Yes	No	Mediastinal LN and bone	Mediastinal LN
3	74	F	White	CHB	Yes/No	42/37	Basal to mid IL and IS	Focal	2.8	No	No	No	Mediastinal LN
4	76	F	White	CHB	No/Yes	67/58	Basal AS, mid IL, mid S	Focal	3.7	No	No	Mediastinal, abdominal LN and lungs	Mediastinal LN
5	54	F	White	CHB, VT	No/Yes	61/63	Basal AS, mid S	Focal	2.5	Yes	No	No	Skin
6	59	M	White	Pulmonary disease	No/No	68/63	Basal S	Focal on diffuse	4.8	No	No	No	Mediastinal LN
7	59	F	Other	Pulmonary disease	No/No	73/61	Basal S, basal to mid AL	Focal on diffuse	2.1	No	No	Lungs, bone, mediastinum, abdominal LN	Mediastinal LN
8	61	F	Black	Pulmonary disease	No/No	31/46	Basal to mid IL	Focal	4.1	No	No	Axillary and hilar LN	Bone marrow
9	56	F	White	CHB	No/Yes	35/28	Basal AS	Focal	2.5	Yes	No	No	Mediastinal LN
10	66	M	White	Pulmonary disease	No/No	56/47	Mid IS	Focal	2.2	Yes	Yes	Mediastinal and hilar LN	Endomyocardial
11	55	M	White	Symptomatic PVCs	No/No	64/64	Basal to mid S	Focal	2.5	Yes	No	Hilar LN	Mediastinal LN
12	69	F	White	Skin disease	No/No	80/60	Basal to mid AS	Focal	6.7	No	No	No	Skin
13	55	F	White	Syncope	No/No	83/65	Basal to mid AS and IL	Focal on diffuse	8.5	No	No	Hilar LN	Conjunctiva

* AF=atrial fibrillation, AL=anterolateral, AS=anteroseptum, CHB=complete heart block, FDG=fluorodeoxyglucose, ICD=implantable cardiac defibrillator, IL=inferolateral, IS=inferoseptum, LN=lymph nodes, LV=left ventricle, LVEF=left ventricular ejection fraction, PM=perfusion-metabolism, PPM=permanent pacemaker, PVCs=premature ventricular contractions, RV=right ventricle, S=septum, SUV=standardized uptake value, VT=ventricular tachycardia

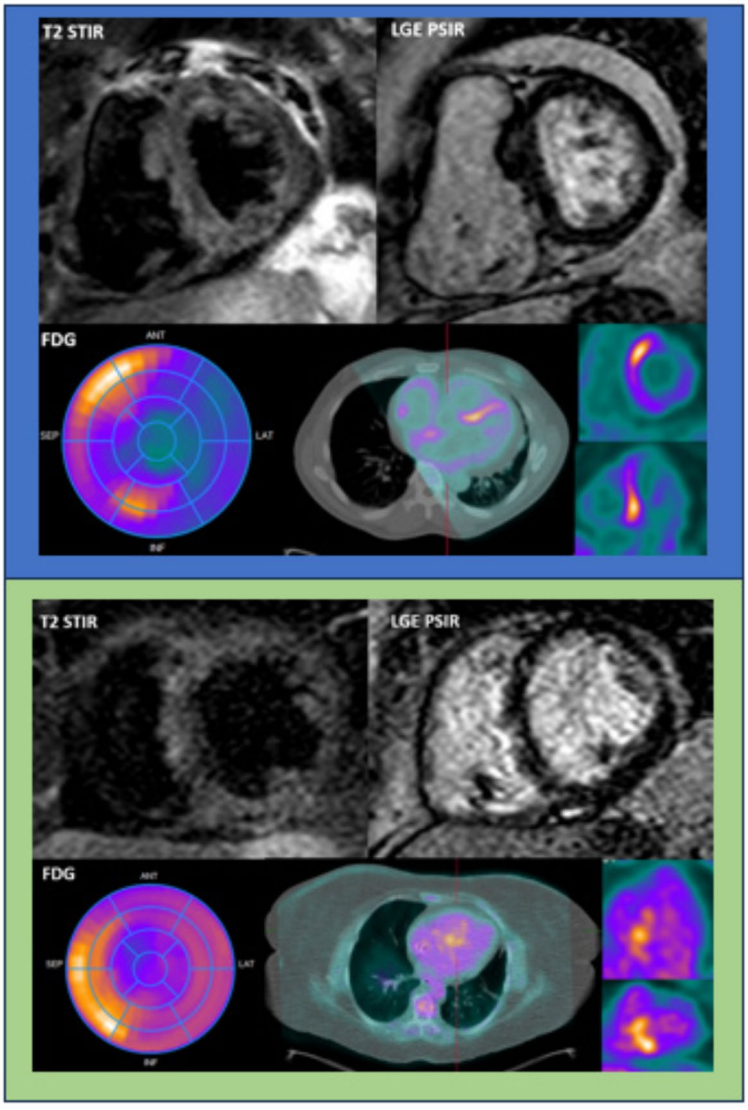

Fig. 1 Graphical abstract. Illustrative case demonstrating discordant inflammation by ^{18}F-FDG PET-CT and CMR in patient 1 (upper panel) and 3 (lower panel)

patients with positive PET-CT but normal tissue characterization by CMR (chi-square p-value=0.08).

In a retrospective observational study of patients undergoing baseline and follow-up simultaneous CMR and PET-CT for evaluation of CS, the CMR to PET-CT discordance was reported to be 32% with 6 studies (19%) showing abnormal myocardial ^{18}F-FDG uptake with no detectable LGE (Coulden et al. 2020). In addition, they found that myocardial ^{18}F-FDG uptake regressed or resolved with treatment in all cases while LGE or myocardial edema on T2-weighted imaging did not change in cases with abnormal tissue characterization by CMR (Coulden et al. 2020). This study suggested better sensitivity for disease monitoring with PET-CT as compared to CMR. Moreover, the ability of PET-CT to evaluate extracardiac disease activity provides an important advantage. Nonetheless, with the increasing shift from T2-weighted imaging with T2-STIR to T2-mapping for assessing myocardial edema with CMR, the sensitivity of CMR for evaluation of acute inflammatory cardiomyopathy may improve (O'Brien et al. 2022). In

our cohort, only 2 of 13 had T2 mapping which may not reflect a contemporary CMR practice. Finally, we observed that this patient population had a favorable prognosis when compared to patients with concordant PET-CT and CMR findings, which may be explained by the lack of fibrosis/LGE, previously shown to be the strongest predictor of mortality and tachyarrhythmia (Hutt et al. 2023).

Our observation that some patients with CS have evidence of disease activity on PET-CT, but not on limited CMR without mapping suggests that a negative limited CMR may not fully exclude CS. Given that this cohort appears to be a relatively low-risk population, we hypothesize that these patients may be in the early phase of CS with inflammation but without development of fibrosis. Thus, although prospective studies are required to address the best imaging approach in cardiac sarcoidosis, our findings suggest that PET-CT should be included in the assessment of disease activity at baseline.

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Author contributions
all authors have made substantial contribution to the concept or design of the article; or the acquisition, analysis, or interpretation of data for the article; and drafted the article or revised it critically for important intellectual content; and approved the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability
Data available on request due to privacy/ethical restrictions.

Declarations

Ethics approval and consent to participate
This work involved human subjects in the form of a registry. Informed consent was waived due to minimal risk as per local IRB standards (IRB number 19-1136).

Consent for publication
Consent for publication was waived due to minimal risk.

Competing interests
The authors have nothing to disclose.

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