JACC: CASE REPORTS VOL. 2, NO. 10, 2020

MINI-FOCUS ISSUE: HEART FAILURE

INTERMEDIATE

CASE REPORT: CLINICAL CASE

Infliximab Treatment of Refractory Cardiac Sarcoidosis

Majid Asawaeer, MD,[a] Benjamin Widener, MD,[b] Varda Singhal, MBBS,[a] Matthew J. DeVries, MD,[c] Debra J. Romberger, MD,[d] Alan R. Erickson, MD,[b] Yiannis S. Chatzizisis, MD, PhD[a]

ABSTRACT

Treatment of cardiac sarcoidosis is challenging, as the disease can be refractory to traditional treatment with steroids. Infliximab, a tumor necrosis factor-α inhibitor, has been reportedly used in cardiac sarcoidosis, but published evidence is limited. The potential cardiotoxicity of infliximab and the Food and Drug Administration black-box warning for patients with heart failure have hindered the use of this agent in cardiac sarcoidosis. Here, we report a case of refractory cardiac sarcoidosis successfully treated with infliximab and discuss the important role of fluorine-18–fluorodeoxyglucose positron emission tomography in prognostication and guidance of therapy. (**Level of Difficulty: Intermediate.**)
(J Am Coll Cardiol Case Rep 2020;2:1553–7) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 63-year-old male patient with biopsy-proven pulmonary sarcoidosis and clinical suspicion of cardiac involvement was referred to our cardiac sarcoidosis (CS) clinic at the University of Nebraska Medical Center, Omaha, Nebraska. He had episodic atypical chest pain and palpitations. His cardiac examination was normal. An electrocardiogram showed normal sinus rhythm with no conduction abnormalities. A transthoracic echocardiogram showed normal left ventricular systolic function without major valvular abnormalities and normal global longitudinal strain (−20%).

LEARNING OBJECTIVES

- CMR and ^{18}F-FDG PET are instrumental in the diagnosis of CS.
- Serial ^{18}F-FDG PET plays a key role in guiding the therapeutic strategy of CS.
- TNF-α inhibitors (i.e., infliximab) can be considered as second- or third-line therapy in refractory CS.

PAST MEDICAL HISTORY

The patient had history of hypertension, hypothyroidism, and pulmonary sarcoidosis. He never smoked and had no family history of cardiac disease or sarcoidosis.

DIFFERENTIAL DIAGNOSIS

Our patient presented with atypical chest pain and occasional palpitations. These otherwise atypical symptoms could occur in a broad spectrum of diseases, including myopericarditis, myocardial

From the [a]Division of Cardiovascular Medicine, University of Nebraska Medical Center, Omaha, Nebraska; [b]Division of Rheumatology, University of Nebraska Medical Center, Omaha, Nebraska; [c]Division of Radiology, University of Nebraska Medical Center, Omaha, Nebraska; and the [d]Division of Pulmonary and Critical Care Medicine, University of Nebraska Medical Center, Omaha, Nebraska. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received May 15, 2020; accepted June 17, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.06.041

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CS = cardiac sarcoidosis

^{18}F-FDG = fluorine-18-fluorodeoxyglucose

PET = positron emission tomography

TNF = tumor necrosis factor

ischemia, pleurisy, and musculoskeletal involvement. The biopsy-proven lung sarcoidosis raised the suspicion of symptomatic cardiac involvement, which occurs in approximately 5% of patients with pulmonary sarcoidosis (1). Myopericarditis and myocardial ischemia were ruled out with echocardiography and exercise stress echocardiography, respectively. Musculoskeletal causes of chest pain were ruled out by history and physical examination.

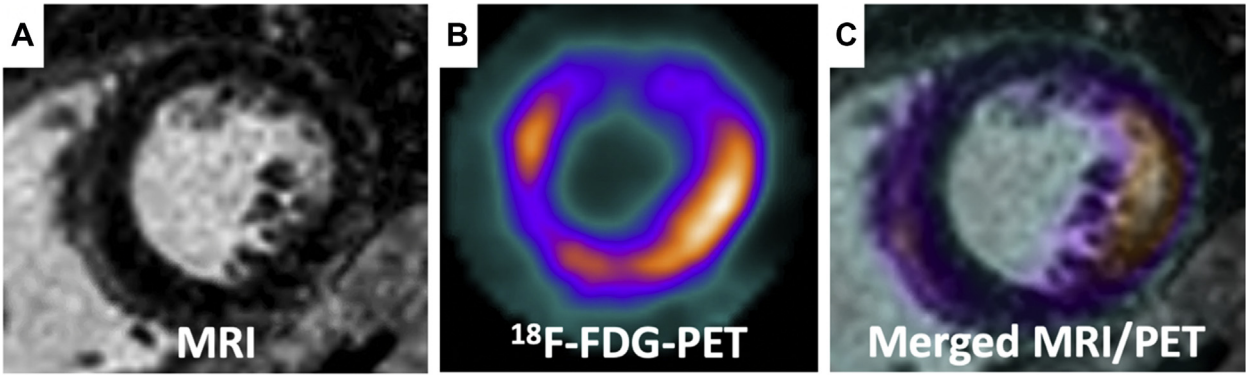
INVESTIGATIONS

We obtained a cardiac magnetic resonance (CMR) scan that showed evidence of mid-myocardial late gadolinium enhancement at the basal septal wall, suggestive of CS (Figure 1A). To investigate the CMR findings further and stage CS, we obtained a fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scan (Figure 1B), which showed basal septal FDG uptake co-localizing with the late gadolinium enhancement on CMR (Figure 1C), a finding highly suggestive of the early active stage of CS.

MANAGEMENT

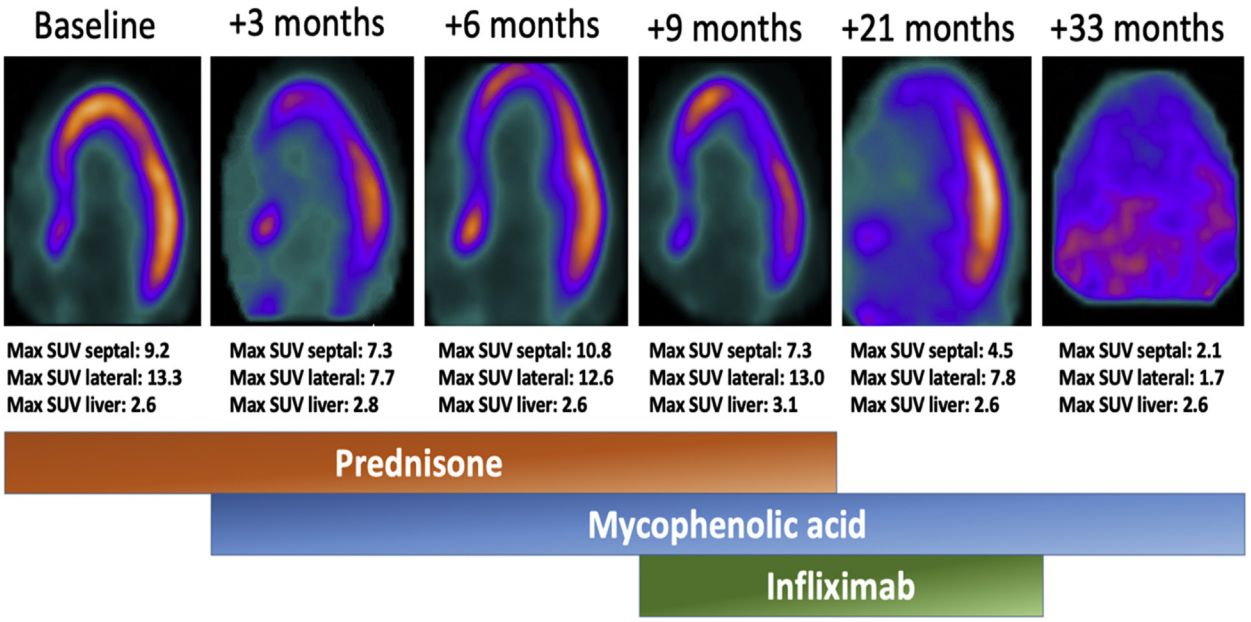
The patient was already receiving steroid therapy for pulmonary sarcoidosis. Given the presence of late gadolinium enhancement on CMR and the history of palpitations, the patient underwent an electrophysiology study, which had negative results. Implantable cardioverter-defibrillator insertion was not pursued (2). A repeat ^{18}F-FDG PET scan at 3 months after the diagnosis of CS showed unchanged FDG uptake extending to the lateral wall and apex of the heart (Figure 2). At that point we added mycophenolate mofetil and continued the steroid therapy. Repeat ^{18}F-FDG PET at 6 months from the diagnosis of CS showed worsening FDG uptake (Figure 2). Given the refractory status of CS and the patient's worsening chest pain, the decision was made to initiate therapy with infliximab, a tumor necrosis factor (TNF)-α) inhibitor. The risks and benefits of the drug were discussed with the patient in our joint CS and rheumatology clinic. Serial ^{18}F-FDG PET scans at 9, 21, and 33 months from the diagnosis of CS showed gradual improvement and finally complete resolution of cardiac inflammation (Figures 2 and 3). Clinical improvement was also noted. Notably, pulmonary sarcoidosis showed total resolution by chest radiography (Figure 4). The patient's left ventricular systolic function remained within the normal range on serial transthoracic echocardiograms throughout the course of therapy. After complete resolution of cardiac inflammation, the patient entered the maintenance stage with mycophenolate mofetil therapy only (Figure 2).

FIGURE 1 Cardiac Magnetic Resonance and ^{18}F-FDG PET in CS



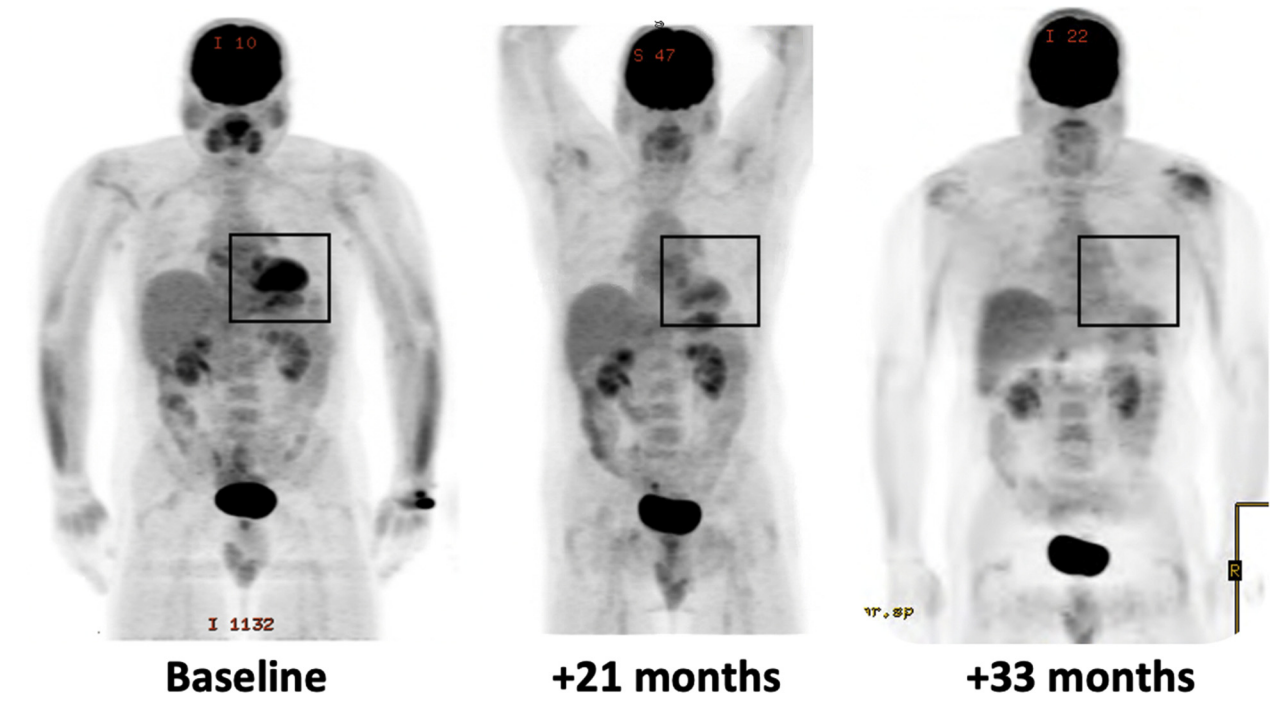
(A) Cardiac magnetic resonance and **(B)** fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) imaging and **(C)** their superimposition at baseline showing co-localization of late gadolinium enhancement with fluorine-18-fluorodeoxyglucose in the basal or midseptal and lateral walls. CS = cardiac sarcoidosis; MRI = magnetic resonance imaging.

FIGURE 2 Serial Cardiac ^{18}F-FDG PET in CS



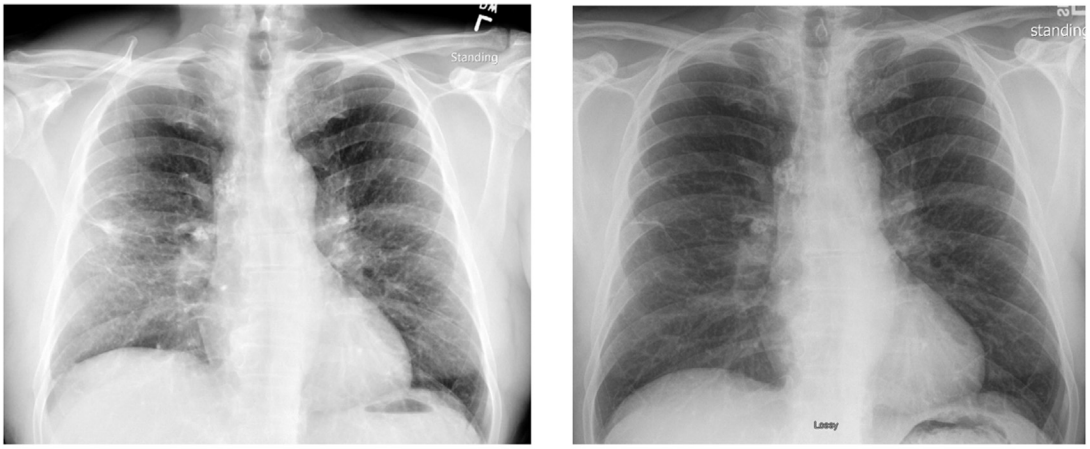
The scans show the qualitative and quantitative response of cardiac sarcoidosis (CS) to escalating anti-inflammatory therapies. Max SUV liver values show standardization of the background glucose uptake. Max = maximum; SUV = standardized uptake value; other abbreviations as in Figure 1.

FIGURE 3 Whole body ^{18}F-FDG PET (Coronal Plane) at Baseline and at 21 and 33 Months After CS Diagnosis



The images show gradual improvement and finally complete resolution of cardiac inflammation. Abbreviations as in Figure 1.

FIGURE 4 Interval Improvement of Pulmonary Sarcoidosis Shown by Chest Radiographs at Baseline and at 21 Months



FOLLOW-UP

We plan to follow up with a final ^{18}F-FDG PET scan at 40 months post-diagnosis of CS.

DISCUSSION

This case highlights 2 important aspects of the diagnosis and therapy of CS. CMR and ^{18}F-FDG PET are complementary to each other in the investigation of suspected CS. Sometimes, 1 test can have positive results and the other negative, so both tests should be performed for the initial CS diagnosis (3). Studies showed that ^{18}F-FDG PET has good sensitivity (89%), but low specificity (33.3%) for the diagnosis of CS (4). After the diagnosis of CS is established, serial ^{18}F-FDG PET is the best approach to assess disease activity and response to therapy (3). Although CMR has a potentially superior negative predictive value in the initial evaluation of suspected CS compared with^{18}F-FDG PET, it cannot provide reliable longitudinal monitoring of disease activity (5). The ability to quantify FDG uptake in CS is the foundation for the most important advantage of ^{18}F-FDG PET over CMR in CS imaging (2,3). The reproducibility of FDG PET without clinical or therapeutic changes between studies has been reported in publications. Adherence to a strict high fat, low carbohydrate diet preparation protocol (Supplemental Appendix) and extension of FDG incubation time to 120 min improve cardiac FDG reproducibility (6).

CS is sometimes difficult to control with steroid treatment, the first-line therapy (refractory CS). Treatment of refractory CS is not well established because of a lack of randomized controlled trials. In refractory CS, biological agents, including TNF-α inhibitors, can be considered for second- or third-line therapy. Case series and observational studies have demonstrated an encouraging response of CS to TNF-α inhibitors. However, the potential for worsening heart failure with any of the TNF-α inhibitors remains a considerable concern. In the ATTACH (Anti-TNF Therapy Against Congestive Heart Failure) trial, where patients with congestive heart failure were treated with infliximab, infliximab increased all-cause mortality and hospitalizations (7). The RENEWAL (Randomized Etanercept Worldwide Evaluation) trial failed to show any clinically-relevant benefit in congestive heart failure with targeted anticytokine therapy with etanercept, a soluble TNF antagonist (8). However, the results of the ATTACH and RENEWAL trials cannot be generalized to patients with normal left ventricular function or cardiomyopathy secondary to sarcoidosis. A recent cohort analysis showed significant improvement of CS with infliximab without worsening systolic function (9). In line with the findings of this cohort, our case report suggests that infliximab may be a promising second- or third-line therapy for patients with refractory CS.

CONCLUSIONS

CMR and ^{18}F-FDG PET are indispensable tools in the initial diagnosis of CS. ^{18}FDG PET offers quantifiable monitoring of disease activity and response to therapy, thereby enabling prompt identification of patients with steroid-refractory CS who could benefit from escalation of anti-inflammatory therapy.

Infliximab may be a promising second- or third-line therapy for patients with refractory CS. Future randomized clinical trials are warranted to determine the safety and efficacy of infliximab and other TNF-α inhibitors in CS.

ADDRESS FOR CORRESPONDENCE: Dr. Yiannis S. Chatzizisis, Cardiovascular Division, University of Nebraska Medical Center, Omaha, Nebraska 68198. E-mail: ychatzizisis@icloud.com.

REFERENCES

1. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis-state of the art review. Cardiovasc Diagn Ther 2016;6:50–63.

2. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm 2014;11:1305–23.

3. Bravo PE, Singh A, Di Carli MF, Blankstein R. Advanced cardiovascular imaging for the evaluation of cardiac sarcoidosis. J Nucl Cardiol 2019;26:188–99.

4. Divakaran S, Stewart GC, Lakdawala NK, et al. Diagnostic accuracy of advanced imaging in cardiac sarcoidosis. Circ Cardiovasc Imaging 2019;12:e008975.

5. Wicks EC, Menezes LJ, Barnes A, et al. Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging 2018;19:757–67.

6. Alvi RM, Young BD, Shahab Z, et al. Repeatability and optimization of FDG positron emission tomography for evaluation of cardiac sarcoidosis. J Am Coll Cardiol Img 2019;12:1284–7.

7. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Anti-TNF Therapy Against Congestive Heart Failure investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–404.

8. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.

9. Harper LJ, McCarthy M, Ribeiro Neto ML, et al. Infliximab for refractory cardiac sarcoidosis. Am J Cardiol 2019;124:1630–5.

KEY WORDS cardiac sarcoidosis, infliximab, magnetic resonance imaging, positron emission tomography

APPENDIX For a supplemental imaging protocol, please see the online version of this paper.