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CASE REPORT

INTERMEDIATE

CLINICAL CASE: EDUCATIONAL CLINICAL CASE SERIES

Inflammatory Cardiomyopathies

A Need to Identify Indolent Inflammation

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ABSTRACT

We present 3 cases of inflammatory cardiomyopathies illustrating the need for a multimodality imaging and multidisciplinary approach for diagnosis and treatment. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2022;4:632-638) © 2022 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/).

Nonischemic cardiomyopathy (NICM) can have diverse underlying causes, including infectious, autoimmune, infiltrative, genetic, and otherwise labeled idiopathic. Timely diagnosis of reversible causes such as inflammation is essential for promoting reversal of heart failure (HF). We present 3 cases of cardiomyopathies to illustrate the need for multimodality imaging (MMI) with multidisciplinary engagement.

PATIENT 1

A 68-year-old White man with history of hypertension and hyperlipidemia received a diagnosis of acute onset HF secondary to NICM 6 months previously. At the time of initial evaluation, the laboratory data revealed a mildly elevated troponin I value of 0.042 ng/mL and a B-type natriuretic peptide (BNP) value of >5,000 pg/mL, but the other serologic work-up results were unremarkable. An echocardiogram showed an ejection fraction (EF) of 20% to 25% (Video 1), and cardiac catheterization showed normal coronary arteries, a Fick cardiac index of 1.5 L/min/m^2, and pulmonary capillary wedge pressure of 22 mm Hg. Guideline-directed medical therapy (GDMT) with carvedilol, sacubitril-valsartan, and spironolactone was initiated but was limited by hypotension. In view of his persistent New York Heart Association functional class III symptoms, the patient was referred for advanced therapies. Cardiac magnetic resonance (CMR) showed scar (14% of myocardium) at the level of basal and mid-interventricular septum and the attached papillary muscles (**Figure 1**). While advanced therapies were being considered, the results of CMR and the short, rapid course of progression raised the suspicion of an inflammatory origin. Fluorodeoxyglucose (FDG)

LEARNING OBJECTIVES

- To identify the role of indolent inflammation as a cause of NICM.
- To understand the NICM work-up using MMI.

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positron emission tomography (PET) demonstrated inflammation in 95% of the left ventricle (LV) (Figure 2). An electroanatomic mapping (EAM)-guided biopsy of the LV revealed minimal focal interstitial edema. Given the discordant results, the patient underwent repeat FDG PET 1 week later with a more prolonged preparation (to ensure that the study result was not false positive), and it showed inflammation involving 37% of the LV. On the basis of the degree of inflammation and the potential need for advanced therapies, we conducted a multidisciplinary patient-centered discussion that led to the final care plan: a course of high-dose intravenous induction steroids followed by a slow oral taper over 3 months. In 3 months, the patient had complete resolution of his dyspnea and abdominal fullness, as well as recovery of his functional status with concomitant normalization of the EF (Video 2). A repeat FDG PET showed complete resolution of the inflammation.

PATIENT 2

An 84-year-old White woman with hypertension received a diagnosis of NICM during an investigation of frequent premature ventricular contractions (PVCs) on a preoperative electrocardiogram before an orthopedic operation. She was asymptomatic at this time, without any dyspnea or palpitations. The initial laboratory data revealed a BNP value of 421 pg/mL, but the other work-up results were unremarkable. Echocardiography revealed a reduced EF (35%-39%), an angiogram showed normal coronary arteries, and the patient was started on metoprolol succinate at 25 mg daily. Unfortunately, her dyspnea worsened, and CMR was performed. The imaging showed a dilated LV with a patchy, non-coronary artery disease scar (1% myocardium) in the basal inferoseptal wall

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMR = cardiac magnetic resonance

EF = ejection fraction

EAM = electroanatomic mapping

FDG = fluorodeoxyglucose

GDMT = guideline-directed medical therapy

HF = heart failure

LV = left ventricle

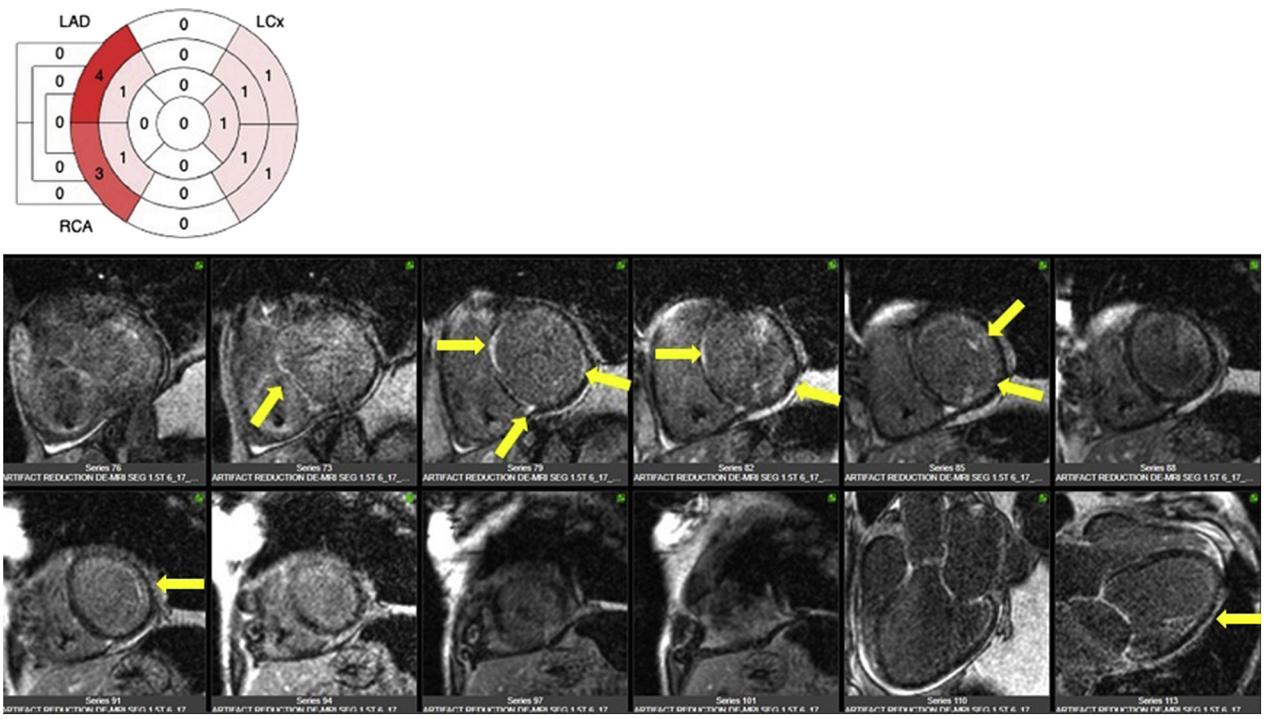
MMI = multimodal imaging

NICM = nonischemic cardiomyopathy

PET = positron emission tomography

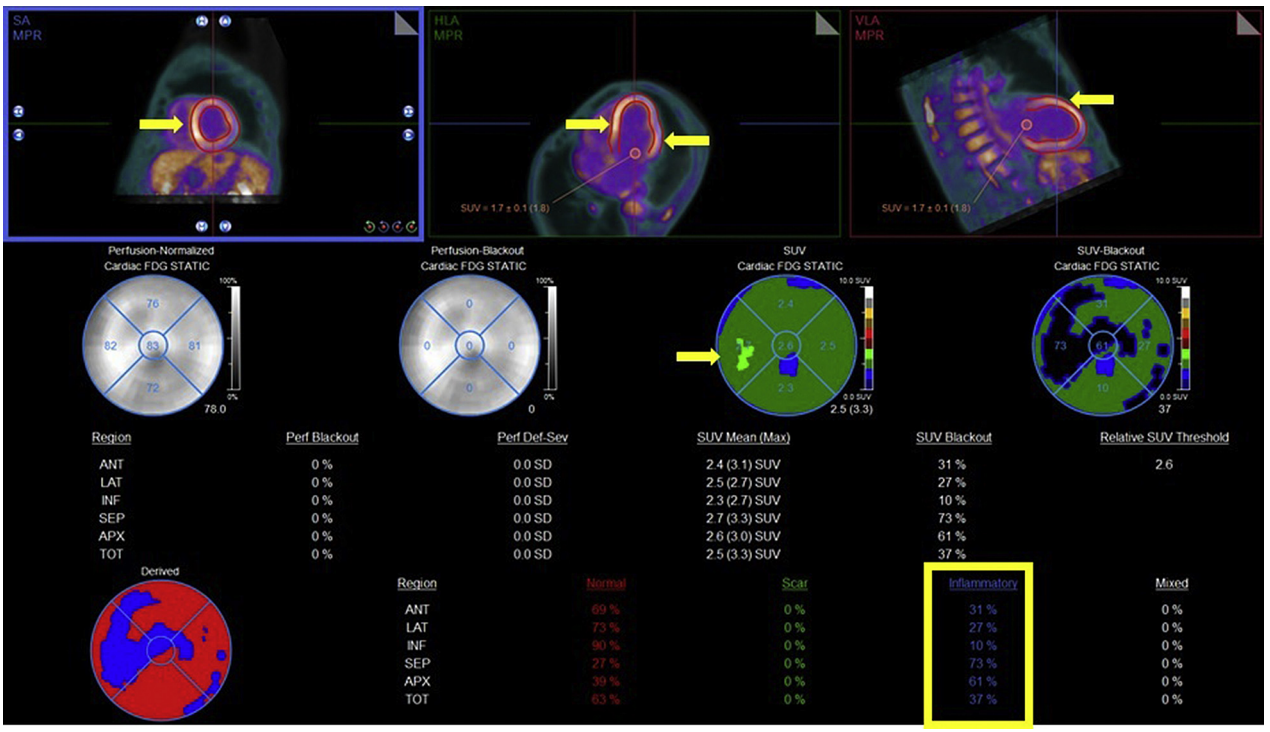
PVC = premature ventricular contraction

FIGURE 1 CMR for Patient 1



Cardiac magnetic resonance (CMR) demonstrated late gadolinium enhancement in the septum, lateral wall, and the papillary muscles, involving 14% of the myocardium. The **yellow arrows** point to the areas of late gadolinium enhancement. DE-MRI = delayed enhancement magnetic resonance imaging; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

FIGURE 2 FDG PET for Patient 1



Fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrated significant active inflammation, correlating to maximum standardized uptake value (SUV [max]) = 3.3 involving 37% of the left ventricle. The **yellow arrows** point to the areas of increased fluorodeoxyglucose uptake. ANT = anterior; APX = apex; INF = inferior; LAT = lateral; Perf = perfusion; SEP = septum; SUV = standardized uptake value; TOT = total.

(Figure 3). FDG PET performed in the context of multiple PVCs (12,000 in 24 hours) revealed an increased uptake of tracer in the basal inferior septum and entire lateral wall (Figure 4). An EAM-guided biopsy performed during PVC ablation demonstrated evidence of lymphocytic myocarditis. The patient was subsequently treated with pulse oral steroids followed by a slow taper of prednisone over 6 months. Repeat FDG PET demonstrated complete resolution of inflammation (Figure 5), and EF was also normalized on repeat CMR (Video 3).

PATIENT 3

A 61-year-old woman with a history of hypothyroidism received a diagnosis of NICM (EF 25%-29%) in the setting of peripheral edema for a few years followed by worsening dyspnea in the past year. She was intolerant to GDMT and progressively unable to work and hence was referred for heart transplantation evaluation. CMR showed a mid to apical scar in the epicardial-midmyocardial distribution encompassing 30% of the LV (Video 4). FDG PET revealed a nontransmural scar encompassing 30% of the LV with nonspecific uptake suggestive of inflammation. Standard biopsy of the right ventricle showed myocardial hypertrophy, interstitial fibrosis, and an aggregate of eosinophils admixed with fibrin without evidence of granulomas. She also had peripheral eosinophilia (27%), elevated C-reactive protein (1.25 mg/dL), mildly elevated BNP (286 pg/mL), but a normal erythrocyte sedimentation rate (1 mm/h). A bone marrow biopsy demonstrated increased (30%) eosinophils, and results of genetic testing for hypereosinophilic syndromes were negative. She was treated with prednisone with normalization of peripheral eosinophil count and improvement in symptoms. After several months, she had worsening functional status with low cardiac output requiring inotropic support and, finally, orthotropic heart

transplantation. The explanted heart demonstrated myocyte hypertrophy with irregular and enlarged nuclei and focal interstitial fibrosis with no specific pathologic process.

DISCUSSION

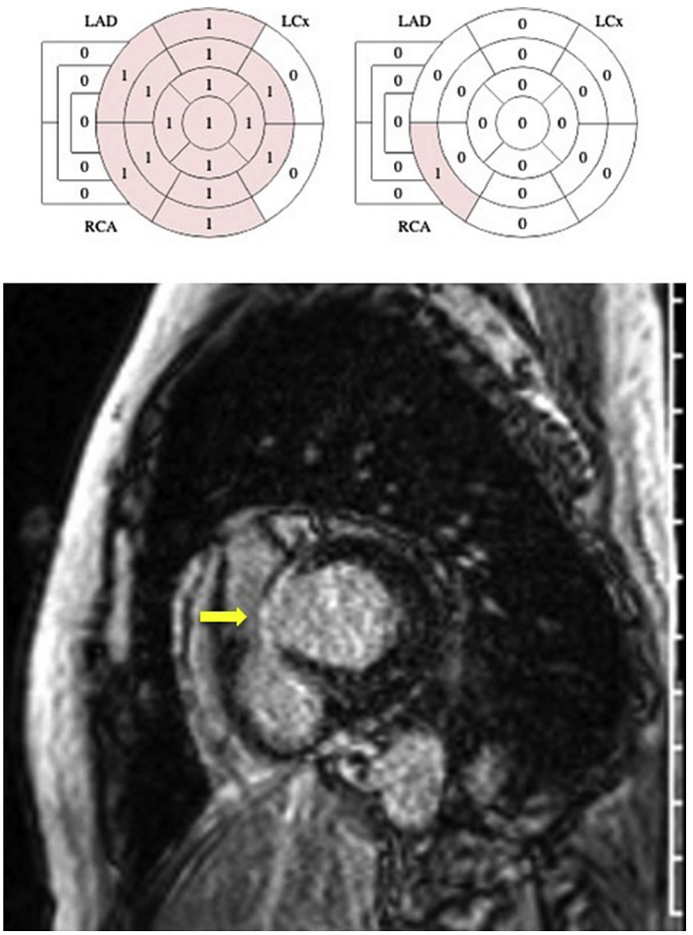
Our cases demonstrate the concept of indolent inflammation and its role in NICM. **Table 1** shows the characteries of the inflammatory cardiomyopathies presented here, characteristics that distinguish such entities from acute myocarditis. Although the history and physical examination can provide clues to the diagnosis of the underlying condition, our patients did not show any evidence of constitutional symptoms or extracardiac (eyes, skin, lungs, central nervous system) signs, and they denied history of exposure to drugs known to cause cardiotoxicity or hypersensitivity. In these cases, a timely diagnosis of active inflammation by using MMI was essential. This diagnosis led to anti-inflammatory treatment beyond GDMT and, ultimately, reversal of the cardiomyopathy. In patient 3, the prolonged course of illness without treatment of active inflammation may have contributed to the extensive scar formation.

CMR identifies interstitial expansion by uptake of gadolinium contrast material, and certain patterns can suggest specific causes of NICM.[1] Whereas interstitial uptake of gadolinium represents collagen deposition (scar) or actively infiltrating cells, FDG PET complements CMR by distinguishing active inflammation from scar. Endomyocardial biopsy is underused in the work-up of NICM despite guideline recommendation,[2] potentially because of poor sensitivity of standard right ventricular septum biopsy (especially for diseases with patchy myocardial involvement). The sensitivity of targeted biopsies using imaging and EAM guidance has been shown to be better,[3] but this procedure is not universally available.

There is limited awareness in the medical community of the need to investigate idiopathic cardiomyopathies further and promptly and to a suspect inflammatory origin in patients with suggestive findings on imaging (**Table 1**). Furthermore, as reflected in patient 1, limitations in our understanding of inflammatory cardiomyopathies complicate clinical decision making. Even with a negative biopsy result, a clinical decision was made to treat the patient with an anti-inflammatory strategy, leading to successful recovery from NICM. This case could also illustrate the need to improve targeting (optimal EAM thresholds, or combining EAM and imaging) for biopsies and to perform specialized staining and processing of the biopsy specimens beyond classic hematoxylin and eosin staining. Studies showing the role of noncellular components of the immune system and various types of immune cells causing myocardial dysfunction[4] clearly document a need to expand our understanding of the biology of idiopathic NICMs beyond the current neurohormonal and genetic pathophysiology.

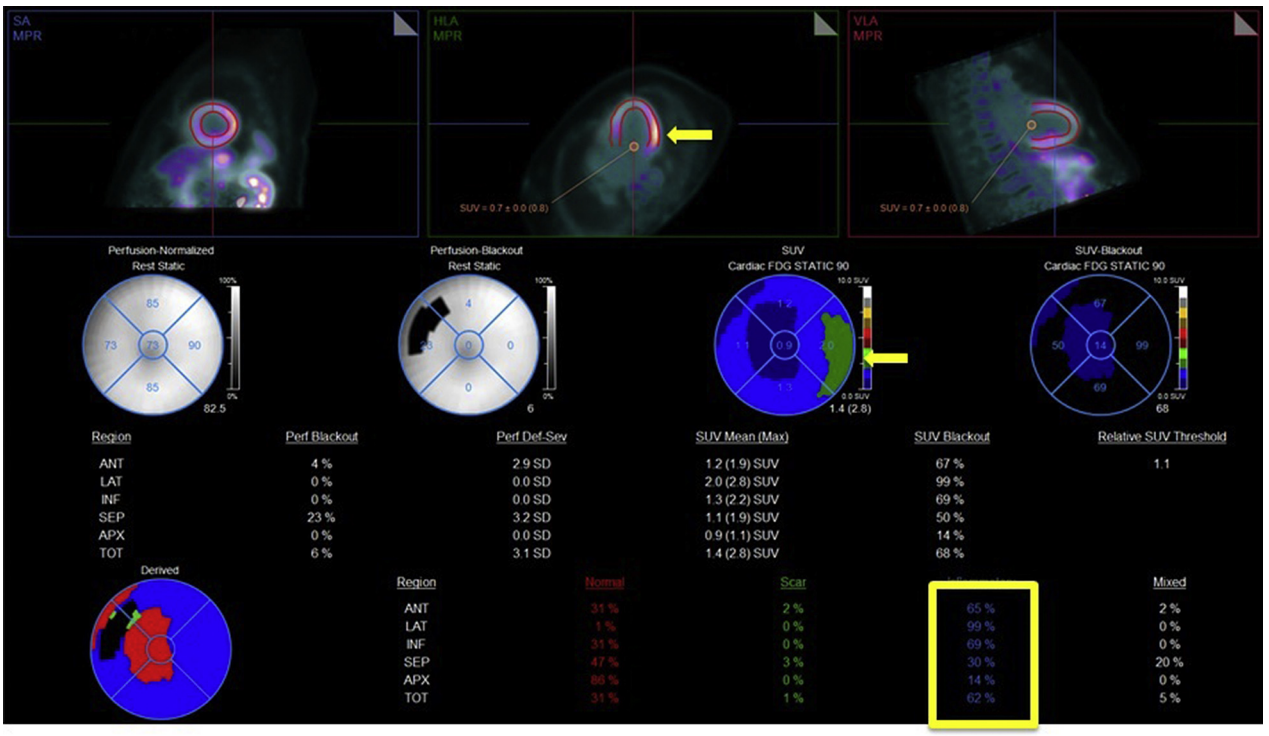
Current guidelines on work-up of inflammatory cardiomyopathies have not captured the recent advancements in imaging modalities.[2,5] Although CMR use is increasing in the work-up of cardiomyopathies, there is no clear recommendation for its early use in

FIGURE 3 CMR for Patient 2



Cardiac magnetic resonance (CMR) demonstrated late gadolinium enhancement in the basal inferoseptal wall, involving 1% of the myocardium. The **yellow arrow** points to the areas of late gadolinium enhancement. Abbreviations as in **Figure 1**.

FIGURE 4 FDG PET for Patient 2



Fluorodeoxyglucose (FDG) positron emission tomography (PET) demonstrated significant active inflammation in the basal inferior septum and entire lateral wall, involving 62% of the left ventricle. The **yellow arrows** point to the areas of increased fluorodeoxyglucose uptake. Abbreviations as in Figure 2.

the diagnosis of NICM. A comparative effectiveness study assessing early investigation with CMR with or without FDG PET along with guided biopsies in the work-up of NICM is an important area for future research. Although these investigations seem expensive, the cost of missed opportunities to modulate the causative factor for HF, thereby resulting in a lifetime of worsening cardiomyopathy as reflected in patient 3, could justify such an investigation and the clinical application of MMI.

There are a few limitations of this case series. First, given the retrospective design of this study, we were not able to obtain a uniform work-up that includes viral serologic examinations, interleukin-6 levels, autoimmune disease markers, and genetic markers. Future prospective trials may be helpful in obtaining such data to complement MMI to diagnose inflammatory cardiomyopathies. Second, the patients in our sample were older, ranging from 61 to 84 years of age, which put them at higher risk of multiple comorbid conditions that can increase systemic inflammation. However, none of these patients, in fact, had other diagnoses of chronic conditions. Future studies can validate our findings in a younger cohort to investigate the generalizability of these observations.

Our case series illustrates the importance of the potential role of inflammation in the etiology of NICM and highlights the need for future studies.

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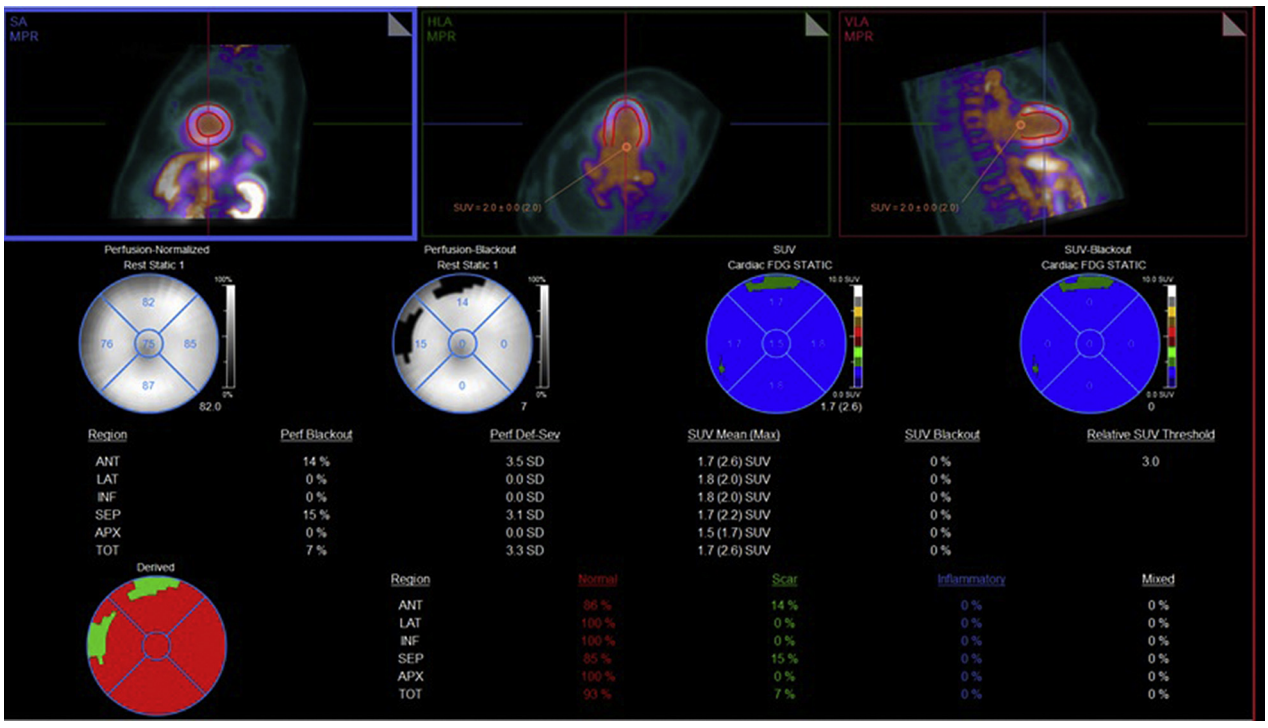
FIGURE 5 **FDG PET for Patient 2**



Fluorodeoxyglucose (FDG) positron emission tomography (PET) after a short course of steroids demonstrated complete resolution of active inflammation. Abbreviations as in Figure 2.

TABLE 1 **Characteristics of Inflammatory Cardiomyopathies**

Type	History and Physical	Laboratory and Imaging	Histopathologic Features	Management
Cardiac sarcoidosis	Indolent course, often present with heart block and ventricular arrhythmias, associated with other noncardiac manifestations such as hilar lymphadenopathy, anterior uveitis, erythema nodosum, and pulmonary hypertension; isolated cardiac involvement is more prevalent than previously thought	Chest radiographic imaging may demonstrate lymphadenopathy; echocardiogram may show hypokinesis or akinesis in the affected walls of myocardium	Noncaseating granulomas in the myocardium; typically, patchy involvement most often in inferior wall or inferoseptum	Steroids followed by other immunosuppressive medications such as methotrexate, mycophenolate mofetil (CellCept), infliximab; many patients need long-term suppression with close surveillance of sarcoid activity
Lymphocytic	Can be acute or indolent; various phenotypes pending the inciting event (eg, autoimmune, viral-associated, or virus-induced)	May see elevated lymphocyte count, respiratory pathogen panel may detect active viral infections, elevated C-reactive protein, or erythrocyte sedimentation rate	Cardiomyocyte necrosis and infiltration of T cells can be demonstrated with immunohistologic staining (eg, anti-CD3 antibody); "starry sky" appearance with lymphocytic infiltrates	Many could resolve without treatment; short course steroids followed by a taper on the basis of clinical syndrome; other immunosuppressive medications and long-term immunosuppressive agents typically not needed
Eosinophilic	Multiple phases: acute phase characterized by cardiogenic shock followed by sometimes valvulopathies, apical obliteration; may be related to hypersensitivity to drugs, parasitic infection, hypereosinophilic syndrome, autoimmune conditions (eg, Churg-Strauss), or idiopathic	Elevated eosinophil count (typically more than 500/μL); echocardiogram may show hypertrophy secondary to edema, or apical obliteration in late stages	Eosinophilic infiltration of the myocardium	Withdraw offending agent if related to drug hypersensitivity; can also treat with steroids, but for refractory cases, anti-interleukin-5 (mepolizumab) can be tried; for eosinophilic syndromes may need long-term immunosuppression with maintenance steroids

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KEY WORDS cardiomyopathy, chronic heart failure, imaging

APPENDIX For supplemental videos, please see the online version of this article.