Case Report

Adalimumab in the treatment of cardiac sarcoidosis: Single center case series and narrative literature review

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ABSTRACT

Background: Tumor necrosis factor (TNF) inhibitors have been used in the treatment of cardiac sarcoidosis, infliximab being the most commonly used. We have previously reported a case of effective treatment of cardiac sarcoidosis using adalimumab.

Objective: To describe our experience of using adalimumab in the treatment of cardiac sarcoidosis.

Methods: We conducted a retrospective study to evaluate patients with cardiac sarcoidosis who received adalimumab treatment at the University of Illinois Health between 2011 and 2022. The outcome was evaluated by assessing safety, tolerability, and ability to taper systemic corticosteroids therapy following initiation of adalimumab.

Results: Seven patients met the inclusion criteria. Clinical responses to adalimumab were universally positive. Corticosteroid therapy was discontinued in five patients and the dose was reduced in two patients. Furthermore, adalimumab was well tolerated, and no adverse events were reported.

Conclusion: Adalimumab was safe and well-tolerated in seven patients with cardiac sarcoidosis seen at our medical center and exhibited corticosteroid-sparing effects. Our observation further warrants large prospective studies to evaluate the safety and efficacy of adalimumab in the treatment of cardiac sarcoidosis.

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1. Introduction

Sarcoidosis, a chronic inflammatory condition characterized by noncaseating granulomatous inflammation and immune dysregulation, has become an increasingly well-known cause of cardiac disease which has been shown to have a worse prognosis compared to patients without cardiac involvement [1]. Treatment of cardiac sarcoidosis is challenging, infliximab is the most commonly used anti-TNF in the treatment of cardiac sarcoidosis. Recently, it was shown that infliximab containing regimens are superior to those containing corticosteroids [2]. We previously reported a case of effective treatment of cardiac sarcoidosis using adalimumab, a fully human anti-TNF agent [3]. Thus, we hypothesized that patients with cardiac sarcoidosis may be responsive to adalimumab therapy. Here, we describe a case series of seven patients with cardiac sarcoidosis who were treated with adalimumab therapy.

2. Patients and methods

This is a retrospective study that describes our experience of patients with cardiac sarcoidosis who received adalimumab therapy at the University of Illinois Health (UIH) between 2011 and 2022. The aim of this study was to describe the safety and tolerability of adalimumab in the treatment of cardiac sarcoidosis. Inclusion criteria included all patients who had the diagnosis of cardiac sarcoidosis and received adalimumab between 2011 and 2022. Patients were identified retrospectively by searching electronic medical records. The study was approved by the University of Illinois at Chicago Institutional Review Board (UIC IRB protocol #2021–0659).

In total, seven patients with cardiac sarcoidosis were identified and their clinical course before and after the initiation of adalimumab therapy was assessed by electronic medical record abstraction. The diagnosis of sarcoidosis was based on ATS/ERS/WASOG criteria and supported by extra-cardiac tissue biopsy [4]. Other causes of granulomas were excluded. The diagnosis of cardiac sarcoidosis was based on clinical presentation as well as advanced cardiac imaging in concordance with both the 2014 Heart Rhythm Society (HRS) expert consensus statement [5] and The Japanese Society of Cardiology expert consensus diagnostic criteria (2017) [6]. Advanced cardiac imaging with $^{18}$fluorodeoxyglucose positron emission tomography (FDG-PET) scans was also performed in all patients as part of the diagnostic and follow-up workup (except for S5 whose last follow-up FDG-PET is still pending). All patients followed a high-fat low-carbohydrate diet that we described in 2017 prior to FDG-PET scans [7] Those are complex patients that required a multidisciplinary team approach including second and third opinions at multiple academic centers. The clinical response was defined as the ability to decrease the need for corticosteroids without worsening of cardiac symptoms, all these patients were treated and followed by the sarcoidosis team at UIC and the response was assessed by a retrospective chart review. The adalimumab regimen was identical to the regimen we used in the clinical trial of pulmonary sarcoidosis [8]. Adalimumab (40 mg subcutaneous injection) was administered on a weekly basis as third-line therapy. The doses of the other immunosuppressants were unchanged for at least 30 days prior to the first adalimumab dose. In accordance with well-accepted clinical practice, all patients received conventional therapy for a duration of at least one year after the diagnosis of cardiac sarcoidosis. In six out of seven patients, therapy was escalated to adalimumab because of persistent cardiac manifestations by FDG-PET despite being on corticosteroid and immunosuppressant therapy. One patient (S5) required escalation to adalimumab while on conventional therapy because of disfiguring skin lesions; however, FDG-PET performed prior to initiation of adalimumab demonstrated cardiac uptake. The clinical characteristics and treatment outcomes are summarized in Tables 1 and 2, respectively. Absolute lymphocyte count in the peripheral blood as well as lymphocyte subset enumeration measured by flow cytometry before and after treatment with adalimumab are shown in Table 3.

3. Results

Clinical responses to adalimumab were universally positive in patients with cardiac sarcoidosis Adalimumab therapy was well tolerated and no adverse events were reported. Five patients discontinued corticosteroids and two patients lowered the dose. Six out of the seven patients had a follow-up FDG-PET scan, two out of the six showed partial resolution of cardiac sarcoidosis compared to the initial FDG-PET-scan and the other four showed complete resolution as shown in Table 2. Of note, none of these patients showed active extracardiac manifestations of sarcoidosis and there were no arrhythmic episodes and hospitalizations while on adalimumab therapy.
between the period 2015–2022. It was noted that all patients showed an increase in their absolute peripheral lymphocytes after adalimumab was initiated (Table 3). The change in absolute lymphocyte, CD4$^+$ T-cell, and CD19$^+$ B-cell count are summarized in Figs. 1 and 2A. Also, S5 showed a steep increase in CD19$^+$ B-cell count as the patient was treated recently and was introduced to adalimumab therapy much earlier given disfiguring facial lesion.

4. Discussion

Infliximab is the only anti-TNF that has been tested in a randomized controlled study in patients with sarcoidosis [9]. We have previously shown the safety and efficacy of adalimumab in a prospective non-randomized clinical trial in pulmonary sarcoidosis [8]. Subsequent studies showed the benefit of using adalimumab in patients who developed adverse events to infliximab in sarcoidosis [10]. The use of anti-TNF remains controversial [11]. Biomarkers that predict response to anti-TNF therapy in sarcoidosis are not well-defined, thus assessing therapeutic response to anti-TNF therapy in cardiac sarcoidosis is challenging. In a post-hoc analysis, we showed that C-reactive protein may predict response of pulmonary sarcoidosis to infliximab therapy [12]. However, biomarkers for response to adalimumab therapy have not been identified. Given the multiple comorbidities in patients with cardiac sarcoidosis and the concern for arrhythmias, we chose the subcutaneous approach using adalimumab to avoid potential infusion reactions and to avoid the possibility of human chimeric antibody (HACA) formation in response to infliximab treatment. Given the difficulties of identifying

### Table 1: Clinical characteristics of patients with cardiac sarcoidosis and lymphopenia receiving adalimumab.

| Patient | Age | Race | Sex | Date of diagnosis of index organ involvement requiring treatment | Cardiac-related signs/symptoms | ICD | Other organ involvement | Index organ involvement requiring treatment | Previous treatment | ADA dose/treatment duration, follow up |
|---------|-----|------|-----|---------------------------------------------------------------|--------------------------------|-----|------------------------|---------------------------------------------|-------------------|----------------------------------------|
| S1      | 61  | Caucasian | M  | Diagnosed in 2012                                           | Cardiac: Shortness of breath (3rd degree AV block) | Yes | Pulmonary (Intrathoracic lymphadenopathy) | Cardiac | CTS and MTX | 40 mg weekly/ Started on 6/2015, From 2015-now |
| S2      | 54  | Caucasian | F  | Diagnosed in 2017                                           | Cardiac: Palpitations (Atrial fibrillation and sinus pauses >13 seconds) | Yes | Pulmonary (Intrathoracic lymphadenopathy) | Cardiac | CTS and MTX | 40 mg weekly/ Started on 11/2020 2020-now |
| S3      | 64  | Caucasian | M  | Diagnosed in 2017                                           | Cardiac: Presyncope episode (3rd degree AV block) | Yes | Spleen | Cardiac | CTS and MTX | 40 mg every other week/ Started on September 2020 |
| S4      | 57  | Caucasian | F  | Diagnosed in 2016                                           | Cardiac: Palpitations (Ventricular tachycardia) | Yes | Pulmonary (Intrathoracic lymphadenopathy) | Cardiac | CTS and MTX | 40 mg every other week/ Started on July 2020 |
| S5      | 55  | Caucasian | F  | Diagnosed in 2020                                           | Cardiac: Presyncope and palpitation (Frequent PVCs) | No | Skin and pulmonary (Intrathoracic lymphadenopathy) | Disfiguring facial skin lesion | CTS and MTX | 40 mg weekly/ Started January 2021 |
| S6      | 65  | Caucasian | F  | Diagnosed in 2014                                           | Cardiac: Shortness of breath and syncope (Ventricular tachycardia) | Yes | None | Cardiac | CTS, MTX and mycophenolate | 40 mg weekly/ Started 4/21/2020 |
| S7      | 73  | Caucasian | F  | Diagnosed in 2013                                           | Cardiac: Cardiac shortness of breath and heart murmur aortic valve insufficiency (3rd degree AV block) | Yes | Pulmonary (Intrathoracic lymphadenopathy) | Cardiac | CTS and MTX | 40 mg weekly/ Started early 2018 |

ADA = Adalimumab; M = male; F = female; ICD = Implantable Cardiac Defibrillator; CTS = Corticosteroids; MTX = Methotrexate; AV = Atrioventricular; PVC = Premature Ventricular Complex.
Table 2
Treatment outcomes in patients with cardiac sarcoidosis and peripheral lymphopenia who received adalimumab.

| Patient | Steroid dosage | EF as measured by Echocardiogram or Cardiac MRI | Advanced cardiac imaging ADA (PET) | SUV max/mean |
|---------|----------------|-----------------------------------------------|-----------------------------------|-------------|
|         | Before conventional treatment | Before ADA | After ADA | Before ADA | After ADA | Before ADA | After ADA |
| S1      | PDN: 10 mg/day | None | 55–60% (Echo) | 55–60% (Echo) | PET (2012): Demonstrated multifocal hypermetabolic activity within the inferior wall of the left ventricular myocardium, consistent with active cardiac sarcoidosis. |
|         | PET (2015): There are multifocal abnormal uptake in the myocardium to suggest an active inflammatory process, consistent with patient’s known history of cardiac sarcoidosis. The most prominent focus located in the mid to proximal septal wall (SUV of 11.7, image 69); another patchy tracer uptake in the mid to proximal inferior wall (image 79, SUV is 8.5); a smaller area in the distal inferolateral wall (image 77, SUV 6.5). |
|         | PET (2018): No evidence of abnormal FDG uptake in the myocardium |
|         | Cardiac SUV max N/A | Hilar metabolic activity SUV max 3.5 |
| S2      | MPS: 40 mg/weekly and 5 mg PDN/day. | None | 53% (MRI) | 53% (MRI) | PET (August 8, 2017): Shows fairly intense uptake in a zone in the lower lateral wall left ventricle. This corresponds to abnormal focus on cardiac MR, compatible with sarcoid involvement. There is also activity in right atrium superiorly in threethe lateral wall at the cavoatrial junction, intra-atrial septum, and posterior wall of the right atrium which are compatible with sarcoid infiltration. |
|         | PET (August 25, 2020): More extensive involvement of the left ventricular myocardium compared to prior PET CT |
|         | PET (February 22, 2021): There is abnormal localization of FDG activity within the left ventricular myocardium in the mid and apical anterolateral wall. This has significantly improved in extent and FDG activity compared to the recent prior F-18 FDG PET/CT from 8/25/2020. The previously identified abnormal activity in the basal septum, right ventricle, and atria has resolved. |
|         | Cardiac SUV max N/A | Cardiac SUV max N/A |
| S3      | MPS: 6 mg/day | MPS: 2 mg every other day | 23% (Echo) | 43% (Echo) | PET (June 28, 2017): There is 18 FDG uptake in the myocardium including the anterior wall, anterolateral wall, inferior wall and inferior septum. The myocardial perfusion study of 5/18/2017 demonstrated corresponding perfusion abnormalities in the inferior, anterior and septal regions although the 18 FDG uptake is more extensive than the degree of perfusion abnormalities on that study. |
|         | PET (August 3, 2020): Redemonstration of abnormal myocardial activity as follows: * Along the basal inferoseptal segment * Along the mid and basal septum * Left ventricular anterior basal segment * Inferolateral basal segment Marginal improvement |
|         | PET (April 19, 2022): Interval regression of hypermetabolic activity in the left ventricular myocardium. No PET/CT evidence to suggest active myocarditis/cardiac sarcoidosis. |
|         | Basal inferoseptal segment SUV max 3.6 prior SUV max 4.8 |
|         | The mid and basal septum SUV max 4.0 prior SUV max 4.9 |
|         | Left ventricular anterior basal segment SUV max 3.2 compared to SUV max 3.4. |
|         | Inferolateral basal segment, SUV max 3.8 compared to prior SUV max 3.4. |
|         | Cardiac SUV max N/A |

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## Table 2 (continued)

| Patient | Steroid dosage | EF as measured by Echocardiogram or Cardiac MRI | Advanced cardiac imaging ADA (PET) | SUV max/mean |
|---------|----------------|-----------------------------------------------|-----------------------------------|--------------|
|         | At initiation of ADA | Current Before ADA | After ADA | Before convention treatment | Before ADA | After ADA | Before ADA | After ADA |
| S4      | PDN: 7.5 mg/day | None | 57% (Echo) | 54% (Echo) | PET (November 14, 2016): There is increased myocardial uptake noted in the anterior and anterolateral wall of the left ventricle primarily, with low-level increased uptake also noted in the inferior septal region. On the targeted, reformatted images of the heart, there are similar findings noted, also with increased uptake involving the anterior and anterolateral walls, with less intense increased uptake also noted in a patchy distribution in the septum, as well as mildly increased uptake in the inferior wall. |
|         |                  | Before and after values were in the 60s | N/A | PET (July 31, 2019): Suggestive of active cardiac sarcoidosis. Myocardial findings suggestive of cardiac sarcoid involvement at the anterior wall, septum, apex, and inferior basal wall. |
| S5      | MPS: 6 mg/day | None | Before and after values were in the 60s | N/A | PET (July 12, 2020): There is moderate to intense activity in the lateral wall of the left ventricle. |
| S6      | MPS: Alternating 8 mg with 6 mg daily | PDN: 2 mg daily | 30% (Echo) | 30% (Echo) | PET (July 7, 2014): There is a medium-sized area of reduced perfusion with intense FDG uptake in the basal anterior and inferior segments, suggestive of active inflammation such as sarcoidosis in these segments. More advanced disease with less active inflammation manifested by severely reduced to absent perfusion and mild to moderate FDG uptake may be found in the apex and the entire septum. |
| S7      | MPS: 20 mg/day | None | 30–35% (Echo) | 48% (Echo) | PET (September 28, 2016): Focus of increased metabolic activity along the proximal anterior septum, near aortic root and right atrium, |
|         |                  | Before and after values were in the 60s | N/A | PET (November 26, 2019): There is new intense activity in the base of the left ventricle extending to the interventricular septum. There is new intense activity along the anterior wall of the left ventricle, which is more intense than the proximal portion, and extends distally approaching the apex. There is new intense activity circumferentially along the base of the heart and slightly to the proximal anterior wall. |
|         |                  | Before and after values were in the 60s | N/A | PET (December 6, 2021): No evidence of cardiac sarcoidosis on current exam. No intense metabolic activity is seen within the mediastinum or hilar regions. Physiologic FDG avidity is seen in mediastinal blood pool, myocardium. |
|         |                  | Before and after values were in the 60s | N/A | PET (March 6, 2019): There is no definite increased activity within the pericardium. There is no abnormal activity within the ventricles. There is stable mild hypermetabolic activity |

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Table 2 (continued)

| Patient | Steroid dosage | EF as measured by Echocardiogram or Cardiac MRI | Advanced cardiac imaging ADA (PET) | SUV max/mean |
|---------|----------------|-------------------------------------------------|-----------------------------------|--------------|
|         | At initiation of ADA | Current | Before ADA | After ADA | Before conventional treatment | Before ADA | After ADA | Before ADA | After ADA |
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one validated outcome measure in treating cardiac sarcoidosis and the retrospective nature of this study, we chose to use the safety of adalimumab and the reduction or discontinuation of corticosteroid dose as the outcome to response given the deleterious effects of corticosteroids in sarcoidosis patients [2].

Of note, our cohort consisted mostly of white male patients, a finding consistent with the Zhou et al. study [13]. All patients were receiving corticosteroids and immunosuppressants (second line agents) as shown in Table 1. Moreover, it was noted that all patients have lymphopenia of less than 1.3 kcell/ul within 3 months of initiating adalimumab therapy. Other causes of lymphopenia were excluded. Lymphopenia is a common feature in patients with sarcoidosis [14] and it may correlate with chronically active severe disease [14–16]. We recently reported a relationship between lymphopenia and sarcoidosis disease activity by fluorodeoxyglucose (FDG)-positron emission tomography (PET) [16]. Crouser et al. [17] described five patients with sarcoidosis and lymphopenia who responded to infliximab treatment with cardiac sarcoidosis manifest in three of the patients. It was concluded that lymphopenia identifies a distinct sarcoidosis phenotype that is responsive to anti-tumor necrosis factor (TNF) therapy [17].

Our current practice included evaluation of the lymphocyte subsets in peripheral blood when patients present with an absolute lymphocyte count of less than 1.3 kcell/ul within 3 months.

Adalimumab has been used off-label in the treatment of cardiac sarcoidosis. Table 4 summarizes the published reports using

### Table 3

| Patient | CD3%, Total T-cells | Abs CD3 (CEL/UL) | CD3/CD4%, Total Helper T-cells | Abs CD3/CD4 (CEL/UL) | CD19%, Total B-cells | Abs CD19 (CEL/UL) | Abs lymphocyte count obtained from CBC (kcells/μL) |
|---------|---------------------|------------------|--------------------------------|----------------------|---------------------|------------------|-----------------------------------------------|
| Reference Range | 58–88% | 767–2352 | 25–62% | 538–1501 | 3–25% | 74–672 | 1.3–4.2 |
| S1 Before | 49 | 322 | 45 | 290 | 13 | 93 | 0.7 |
| After | 64 | 770 | 56 | 652 | 18 | 224 | 1.6 |
| S2 Before | 78 | 840 | 61 | 641 | 14 | 153 | 1.1 |
| After | 77 | 1052 | 61 | 829 | 12 | 163 | 1.4 |
| S3 Before | N/A | 451 | 49 | 311 | 8 | 52 | 0.7 |
| After | 75 | 868 | 58 | 674 | 7 | 85 | 1.1 |
| S4 Before | 75 | 656 | 55 | 482 | 8 | 72 | 0.8 |
| After | 82 | 1460 | 61 | 1068 | 8 | 149 | 1.8 |
| S5 Before | 65 | 410 | 45 | 281 | 21 | 134 | 0.4 |
| After | 70 | 1639 | 51 | 1110 | 25 | 620 | 2.1 |
| S6 Before | 70 | 548 | 51 | 402 | 6 | 46 | 0.8 |
| After | 75 | 852 | 52 | 591 | 9 | 97 | 1.1 |
| S7 Before | N/A | 595 | 29 | 212 | 6 | 44 | 0.7 |
| After | N/A | 1929 | 31 | 646 | 2 | 54 | 2.3 |

**Abs** = Absolute; **N/A** = not available; **CBC** = complete blood count.

Fig. 1. Absolute lymphocyte counts (kcells/μL) before and after adalimumab treatment. All subjects demonstrated lymphopenia (absolute lymphocyte counts <1.3 kcells/μL) prior to initiation of adalimumab and with adalimumab a significant increase in absolute lymphocytes was observed (Wilcoxon matched-pairs signed rank test p-value = 0.0156). The median pre-adalimumab absolute lymphocyte count was 0.7 kcells/μL (standard deviation of 0.21), the median post-adalimumab lymphocyte count was 1.6 kcells/μL (standard deviation of 0.47).
adalimumab for the treatment of cardiac sarcoidosis. However, infliximab is the most widely used anti-TNF agent in cardiac sarcoidosis. Harper et al. [18] demonstrated the safety and efficacy of infliximab in cardiac sarcoidosis treatment in their retrospective series of 36 patients with refractory sarcoidosis treated with infliximab. In their study, 24 out of 36 patients showed a favorable response as defined by at least one of the following: steroid dose reduction, improvement in arrhythmia control, or increase in left ventricular ejection fraction without deterioration of systolic function [18]. Similarly, findings from more recent studies further supported the efficacy of anti-TNF therapy in cardiac sarcoidosis patients, the majority of whom received infliximab [19–21]. A recent meta-analysis of the treatment of cardiac sarcoidosis excluded anti-TNF therapy due to the fact that it is used only in refractory cardiac

**Fig. 2.** A. Effect of adalimumab on CD4+ T-cell and CD19+ B-cell counts in peripheral blood. B. Hypothetical mechanism of lymphopenia resolution with adalimumab therapy in cardiac sarcoidosis.

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**Fig. 2.** A. Effect of adalimumab on CD4+ T-cell and CD19+ B-cell counts in peripheral blood. B. Hypothetical mechanism of lymphopenia resolution with adalimumab therapy in cardiac sarcoidosis.

adalimumab for the treatment of cardiac sarcoidosis. However, infliximab is the most widely used anti-TNF agent in cardiac sarcoidosis. Harper et al. [18] demonstrated the safety and efficacy of infliximab in cardiac sarcoidosis treatment in their retrospective series of 36 patients with refractory sarcoidosis treated with infliximab. In their study, 24 out of 36 patients showed a favorable response as defined by at least one of the following: steroid dose reduction, improvement in arrhythmia control, or increase in left ventricular ejection fraction without deterioration of systolic function [18]. Similarly, findings from more recent studies further supported the efficacy of anti-TNF therapy in cardiac sarcoidosis patients, the majority of whom received infliximab [19–21]. A recent meta-analysis of the treatment of cardiac sarcoidosis excluded anti-TNF therapy due to the fact that it is used only in refractory cardiac
The immunopathogenesis of sarcoidosis is complex and the exact mechanism of improvement of lymphopenia following adalimumab therapy remains speculative. It is unknown if peripheral lymphopenia in sarcoidosis identifies a subset of patients who will have a favorable response to anti-TNF therapy. In a phase 4 clinical trial, we identified IL-7R as a biomarker for anti-TNF response in rheumatoid arthritis (RA) peripheral blood mononuclear cells [23]. We previously demonstrated that IL-7R may play a role in sarcoidosis [24]. IL-7 is a novel sarcoidosis cytokine and is a master regulator of lymphocytes [25]. Possible explanations include relief of T cell overactivation in part by rebalancing the expanded innate immune reprogramming seen in a subset of patients with sarcoidosis. The immunopathogenesis of sarcoidosis is complex, while T-cells are one of the major players in the pathogenesis of sarcoidosis B cells play a role in the disease as well [26]. We have shown that B cell-depleting therapy using rituximab may be effective in sarcoidosis [27]. The improvement of CD19⁺ lymphopenia in this cohort further emphasizes the role of B cells in this disease. We hypothesize that T-cell and B-cell trafficking to areas of active granulomas may be regulated by TNF, IL-7 and IL-7R pathway and may be corrected by neutralizing TNF (See Fig. 2B). Such a hypothesis is speculative and requires large randomized controlled trials with a mechanistic arm to identify the actual role of TNF and IL-7R in regulation of granuloma formation and resolution in various sarcoidosis phenotypes. This is of particular value in light of the challenging nature of cardiac sarcoidosis treatment, the lack of a standardized definition of refractory cardiac sarcoidosis, the lack of biomarkers that identify responsive phenotypes, and the lack of FDA-approved therapies.

Our study has several limitations including the retrospective nature of the study and its inherent problems including selection bias, small sample size, and the lack of a control group. Since we are a referral center most patients who are seen already had some initial testing thus, we did not have the absolute lymphocyte count before conventional therapy. While it would be helpful to have baseline absolute lymphocyte counts and flow cytometry prior to conventional treatment and correlate them with inflammation, checking flow cytometry is not standard-of-care without lymphopenia on CBC. It was extremely difficult to standardize the approach to management of cardiac sarcoidosis, especially during the COVID-19 pandemic. Another limitation is the lack of a comparison group without lymphopenia which will require a future multi-center study. Despite these limitations, our observations are consistent with a study.

Table 4

| Author (Reference No.) | Year | Country | Study type | Sample size (N) | Baseline LVEF (%) | Presenting picture of cardiac sarcoidosis | Number of patients receiving adalimumab | Duration of follow up after initiation of anti-TNF-alpha | Concomitant drugs at adalimumab Introduction |
|-------------------------|------|---------|------------|----------------|------------------|------------------------------------------|----------------------------------------|---------------------------------------------|---------------------------------------------|
| Stievenart et al. [28]  | 2021 | France  | Case series | 4              | 60, 66, 30, 26   | Not mentioned                           | 2                                      | 33.8 (16–80) months                      | Methotrexate or azathioprine               |
| Gilotra et al. [19]     | 2021 | USA     | Retrospective multicenter study | 38 | 48⁺            | Ventricular arrhythmia, atrial fibrillation, atrioventricular block, heart failure | 8                                      | median follow-up time of 486 days after TNF alpha inhibitor initiation | Prednisone alone, prednisone and mycophenolate mofetil, prednisone and methotrexate, prednisone and azathioprine |
| Theodore et al. [29]    | 2019 | India   | Case report | 1               | 26               | Ventricular tachycardia (multiple episodes of palpitations) | 1                                      | N/A                                        | N/A                                        |
| Rosenthal et al. [30]   | 2019 | USA     | Retrospective chart review | 28 | N/A            | Atrial arrhythmia, high-grade atrioventricular block, sudden cardiac arrest, heart failure, sustained ventricular tachycardia or ventricular fibrillation | 19                                     | N/A                                        | N/A                                        |
| Krishnan et al. [31]    | 2020 | USA     | Case report | 1               | N/A             | Systolic HF                                                            | 1                                      | 2 years                                   | N/A                                        |
| Baker et al. [20]       | 2020 | USA     | Retrospective single-center study (review) | 77     | 43⁺            | Heart block, tachyarrhythmia (ventricular tachycardia, atrial fibrillation) | 10                                     | 12 months                                 | Methotrexate, prednisone                   |

LVEF = left ventricular ejection fraction; N/A = not available.
⁺ = values are reported as mean left ventricular ejection fraction.
conducted by Judson et al. about steroid-sparing effect of infliximab in cardiac sarcoidosis [2] as well as with those of Crouser et al. [17]. Given the enormous cost associated with advanced cardiac imaging, and the associated radiation exposure, identifying a peripheral biomarker that tracks response to therapy for cardiac sarcoidosis is important. A prospective well-designed translational study in cardiac sarcoidosis is needed to serve this complex patient population.

5. Conclusions

This case series represents a unique cohort of predominantly Caucasian patients with cardiac sarcoidosis who were responsive to adalimumab therapy as measured by improvement in advanced cardiac imaging and the ability to discontinue or reduce corticosteroids. Further Large prospective studies are warranted to determine the safety and efficacy of adalimumab in the treatment of cardiac sarcoidosis.

Clinical perspective

The role of adalimumab in treating patients with cardiac sarcoidosis has not been determined so far. Our small case series describes favorable safety, tolerability, and efficacy profiles of adalimumab in patients with cardiac sarcoidosis.

Translational outlook

Future randomized controlled clinical trials are warranted to determine the safety and efficacy of adalimumab in patients with cardiac sarcoidosis and the mechanisms of improvement of lymphopenia after adalimumab therapy.

Learning points

- In a small retrospective case series, adalimumab was shown to be safe in the treatment of cardiac sarcoidosis.
- Adalimumab showed a steroid-sparing effect in this small case series.
- Lymphopenia is a common feature of sarcoidosis, the effect of anti-TNF therapy on lymphopenia in sarcoidosis patients requires further evaluation.

Guarantor

N. J. S takes responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis.

Author contributions

J. J. S contributed to the conception and design of the research. J. J. S and N. W. S. contributed to data collection, interpretation, table design, figure design, and manuscript drafting. C. A. contributed to data analysis, figure design, and manuscript revision. N. J. S supervised and contributed to all parts of the research. All others contributed to interpretation and provided critical reviews of the manuscript. All authors read and approved the final manuscript for publication.

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Declaration of competing interest

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