SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2025; 42 (3): 16865 DOI: 10.36141/svdld.v42i3.16865

Cardiac sarcoidosis recurrence post-heart transplant: A critical literature and case report

Andrea Salotti[1], Lucrezia Mondini[1], Paola Confalonieri[1], Francesco Salton[1], Chiara Nalli[2], Nicolò Reccardini[1], Chiara Torregiani[1], Caterina Antonaglia[1], Michael Hughes[3], Marco Confalonieri[1], Rossella Cifaldi[1, †], Barbara Ruaro[1, †]

[1]Pulmonology Unit, University of Trieste, Department of Medical Surgical and Health Sciences, Hospital of Cattinara., Trieste, Italy; [2]Cardiothoracic Department, University Hospital of Udine, Udine, Italy; [3]Division of Musculoskeletal and Dermatological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester & Salford Royal NHS Foundation Trust, Mancheste, UK

[†]These authors contributed equally to this work.

Abstract. *Background and aim:* Recurrence of cardiac sarcoidosis (CS) following heart transplantation (HT) is a rare but clinically significant complication that influences management strategies and prognosis. This review examines existing evidence on the diagnosis and treatment of post-transplant CS recurrence. Additionally, we present a case report of CS recurrence in a patient after HT. *Methods:* We analyzed clinical studies, case reports, and systematic reviews published up to January 2025, focusing on the recurrence of CS after transplantation. *Results:* Limited data suggest that immunosuppressive therapies are crucial in managing post-transplant CS recurrence. Diagnosis relies on imaging modalities such as Positron Emission Tomography (PET-CT), Cardiac Magnetic Resonance (CMR), and endomyocardial biopsies. Treatment generally involves intensifying immunosuppressive therapy. *Conclusions:* Standardized guidelines are essential to improve the management of this rare and complex condition and to enhance long-term patient outcomes.

Key words: cardiac sarcoidosis, post-transplant recurrence, immunosuppressive therapies, Positron Emission Computed Tomography (PET-CT), Cardiac Magnetic Resonance (CMR), endomyocardial biopsy

Background

The pathogenesis of sarcoidosis is complex and not fully understood, but it is believed to involve a genetic predisposition, an altered immune response to still-unidentified environmental stimuli, and a dysregulation of the immune system (1-4). Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas that mainly affect the lungs and lymph nodes, although numerous organs and tissues can be involved (1-4). Cardiac involvement (CS) is associated with a worse prognosis (2, 5), with an estimated prevalence between 5% and 25% of patients with sarcoidosis (2, 5-7). The diagnosis of CS is often complex due to clinical variability and overlap with other cardiac pathologies, including dilated, hypertrophic, and arrhythmogenic cardiomyopathies (8). Heart transplant (HT) is generally reserved for patients with advanced heart failure or life-threatening arrhythmias that cannot be adequately controlled with other therapies, such as antiarrhythmic drugs, immunosuppressive therapy, or the implantation of devices such as pacemakers or implantable cardioverter defibrillators. In patients undergoing HT for CS, the risk of CS recurrence in the transplanted heart, although considered rare, with an estimated incidence of less than 10% and a

Received: 7 February 2025
Accepted: 7 April 2025
Correspondence: Prof. Barbara Ruaro, MD, European PhD, Pulmonology Unit, University of Trieste, Department of Medical Surgical and Health Sciences, Hospital of Cattinara, 34149 Trieste, Italy.
E-mail: barbara.ruaro@yahoo.it
ORCID: 0000-0001-8990-859X

variable prevalence between 5% and 18% (9, 7, 10), poses significant challenges for clinical management. Some studies suggest recurrence may occur even earlier than previously thought (11, 12). Post-transplant immunosuppression, necessary to prevent organ rejection, may, in some cases, contribute to the reactivation of residual disease or the formation of new granulomatous lesions in the transplanted heart, as suggested by studies by Seplowe et al. (11, 13, 14). Furthermore, cases of sarcoidosis transmission via cardiac transplantation have been reported (15). The clinical presentation of CS recurrence can include symptoms such as arrhythmias, congestive heart failure, and, in more severe cases, sudden cardiac death. Diagnosis requires a multimodal approach, integrating clinical assessments, electrocardiographic (ECG) findings, advanced imaging such as Positron Emission Tomography-Computed Tomography (PET-CT), Cardiac Magnetic Resonance (CMR), and endomyocardial biopsy to confirm the presence of non-caseating granulomas, although the latter may have limited sensitivity (10, 14, 16, 17). The use of 3D mapping-guided endomyocardial biopsies may improve diagnostic yield (17). The prognosis of patients with post-transplant CS recurrence depends on several factors, including the timing of diagnosis, the extent and severity of the recurrence, the effectiveness of treatment, as well as the presence of transplant-related complications. According to the literature (18), recurrence in a cardiac allograft is possible. Recent studies have shown that patients transplanted for CS do not have significant differences in long-term survival compared to those transplanted for other indications, with 5-year survival rates of 79% (3, 13, 19), although some studies have indicated a trend toward higher mortality in patients with sarcoidosis after transplantation (4, 20). It is important to note that some cases of cardiac sarcoidosis are diagnosed only after heart transplantation, highlighting the challenges in pre-transplant diagnosis (21). In transplanted patients, regular screening and advanced imaging are essential to distinguish CS recurrence from acute rejection, allowing for personalized therapeutic management and optimized clinical outcomes. Furthermore, serum biomarkers like soluble interleukin-2 receptor (sIL-2R) may aid in monitoring treatment response (2). Cardiac involvement without extracardiac manifestations may also occur (22).

Case Report

A 45-year-old Caucasian man, a former smoker with a previous history of recurrent chest pain, heart failure, and ventricular tachycardias, underwent heart transplantation in 2017 because of severe biventricular cardiomyopathy, resulting in impaired cardiac function and life-threatening arrhythmias. In 2016, he underwent a chest computed tomography (CT) scan for pre-transplant tests showing multiple pulmonary nodules, parenchymal consolidation, and mediastinal lymphadenopathy, so a bronchoscopy with trans-bronchial biopsies was performed; furthermore, in May 2017 (before transplantation), he underwent a whole-body PET-CT that revealed hyperabsorption of the radiopharmaceutical in the lungs and lymph nodes, consistent with pulmonary and mediastinal lymph node sarcoidosis. The report did not explicitly mention cardiac uptake. Therefore, a histological diagnosis of pulmonary and lymph node sarcoidosis was made based on lung and lymph node biopsies performed during bronchoscopy, and the patient was treated during the pre-transplant period with prednisone at an initial dosage of 50 mg, progressively tapered. The timing of tapering is not exactly known, as the patient was initially followed at another centre. After HT in 2017, the autopsy of the heart revealed cardiac sarcoidosis. It is debatable whether a dedicated cardiac PET scan at that time would have altered the pre-transplant management, but in retrospect, it might have increased suspicion for CS and potentially influenced post-transplant surveillance strategies. In May 2019 (post-transplant), he underwent a total-body PET-CT in another centre, which revealed hyper uptakes in the heart, both lungs, and mediastinal lymph nodes. Since 2021, the patient began to complain of tachyarrhythmia. He underwent echocardiography and coronary angiography, both normal, and therapy with flecainide was increased. In November 2022, an endomyocardial biopsy was performed on the transplanted heart, with no evidence of disease recurrence. From the perspective of respiratory function, the tests showed a progressive reduction in carbon monoxide (CO) diffusion over time and the appearance of obstructive deficit. Furthermore, in the years following the transplant, he underwent several PET-CT scans that documented a constant level of activity of sarcoidosis at the pulmonary and cardiac levels, but we do not know whether a recurrence of cardiac sarcoidosis was suspected, given that the patient

Table 1. Immunosuppressive therapy for the treatment of sarcoidosis before transplantation, therapy after cardiac transplantation and modification of therapy after diagnosis of recurrence of CS

Pre-transplant	Post-transplant	Post-transplant at CS recurrence
- Prendisone 50 mg, OD *then tapered*	- Cyclosporine 100 mg TD - Mycophenolato Mofetil 750 mg TD - Methylprednisolone 4m OD	- Cyclosporine 100 mg TD - Prednisone 25 mg OD - Methotrexate 10 mg QW

Abbreviations: OD: once daily, TD: twice daily, QW: quaque week, once a week

was not being followed by our center at that time. The echocardiography performed in 2023 revealed septal hypokinesis, indicative of impaired contractility of the left ventricle. The patient, at the time of recurrence, was on maintenance immunosuppressive therapy, which included cyclosporine (100 mg twice daily), mycophenolate mofetil (750 mg twice daily), and methylprednisolone (4 mg daily). For treatment of the recurrence, methotrexate (10 mg/week) was introduced, the dose of steroid (prednisone 25 mg) was increased, and mycophenolate mofetil was discontinued (Table 1).

The therapy was also personalized with anticoagulants and inhaled drugs to manage concomitant ventricular thrombosis and pulmonary involvement. After six months of treatment, the patient showed significant clinical improvement, with a large reduction in inflammatory uptake on PET-CT (Figures 1 and 2, lower panels) and an improvement in the left ventricular ejection fraction (EF) from 35% to 50%, as measured by echocardiography.

Spirometry also improved, with an increase in alveolar-capillary diffusion of CO, which became normal, while the obstructive deficit remained stable, as shown in Table 2. Further indicators of the effectiveness of the therapy were the recovery of good quality of life and the absence of tachyarrhythmia.

Methods

This critical literature review, integrated with a case report, was conducted by analyzing original articles, narrative and systematic reviews, clinical guidelines, and case reports published up to January 2025. The main research sources were the electronic databases PubMed, Scopus, and Web of Science, using relevant keywords, including "cardiac sarcoidosis", "post-transplant recurrence", "immunosuppression", "PET-CT", "cardiac magnetic resonance" and "endomyocardial biopsy." Clinical studies, narrative reviews, and case reports that reported data on the diagnosis, treatment, and prognosis of cardiac sarcoidosis (CS) recurrence after heart transplantation were included. The inclusion criteria comprised: (1) studies on patients undergoing heart transplantation for CS with a confirmed diagnosis of recurrence; (2) studies that described the use of advanced imaging (PET-CT, CMR) and/or endomyocardial biopsies for the diagnosis and monitoring of recurrence; and (3) studies that provided details on the therapeutic regimens used for the management of recurrence. Studies without specific data on post-transplant CS recurrence, studies on unrelated pathologies, and abstracts not published in full were excluded. The selected articles were further divided based on study design, population characteristics, diagnostic methods used, and therapeutic regimens employed to provide a clear synthesis of the most common strategies and to identify the strengths and weaknesses of available evidence. In parallel, a case report of post-transplant CS recurrence at our center was analyzed, with particular attention to the diagnostic process, the therapeutic approach adopted, and the patient's clinical response. This case was chosen as a representative example of the clinical and therapeutic complexities related to the management of recurrent CS. All diagnostic and therapeutic procedures described were performed in accordance with current ethical and clinical guidelines. Data extracted from the literature were organized and synthesized in a narrative review, highlighting both the progress made and the gaps still existing in the understanding of the pathology. Particular attention was paid to the analysis of therapeutic recommendations, with a focus on immunosuppressive therapies, the use of biological therapies, and the multidisciplinary approach (23). The entire process was supervised by a multidisciplinary team comprising cardiologists, pulmonologists, radiologists, and immunologists, ensuring an integrated and multidimensional approach to the literature review and the presentation of the case report.

Results

From the literature analysis, 18 relevant articles were selected: 7 case reports, 4 observational

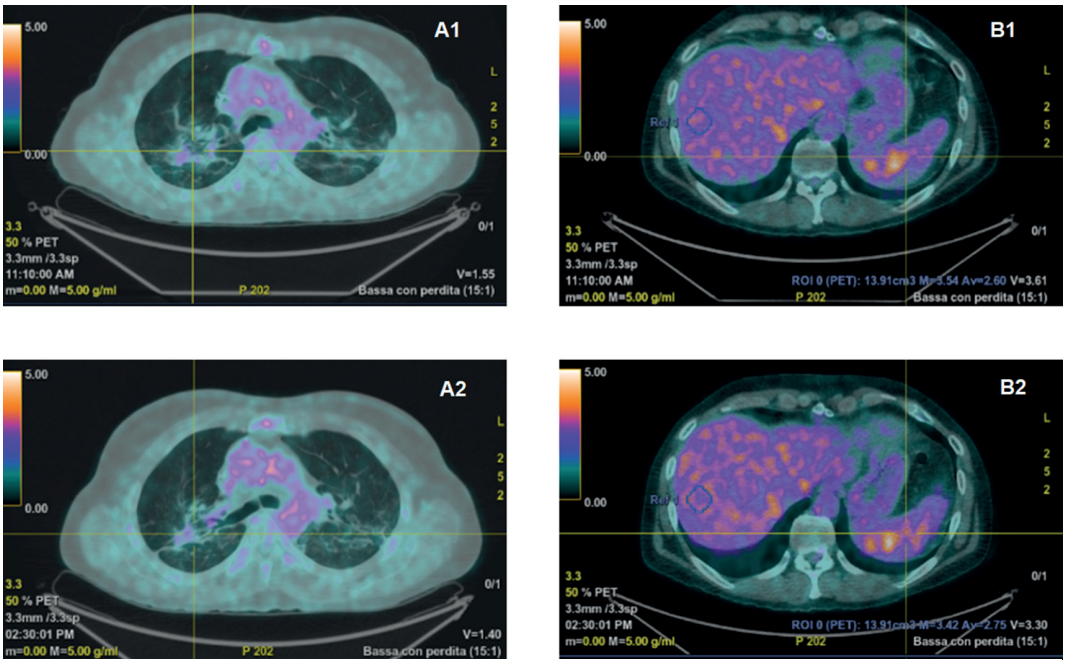

Figure 1. PET/CT scans of the patient before (A1 and B1, left panel) and after (A2 and B2, right panel) therapy for cardiac sarcoidosis recurrence in the transplanted heart: left panel shows lower tracer uptake in the lungs and at splenic levels, the disease remains active, albeit to a lesser extent, even after the first course of therapy.

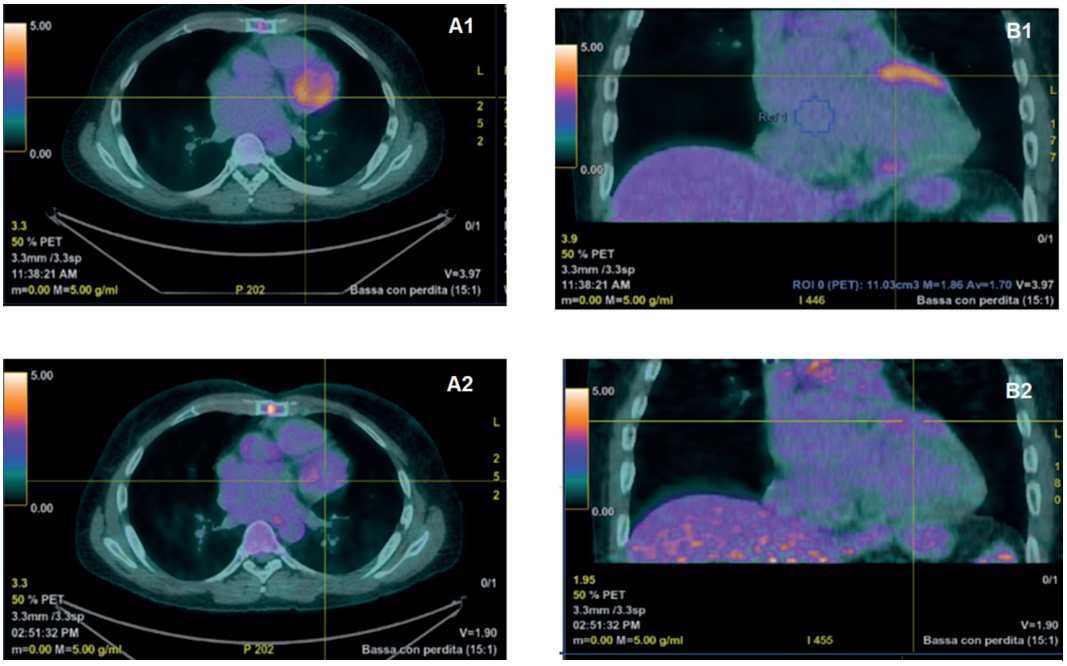

Figure 2. PET/CT scans before (A1 and B1) and after (A2 and B2) therapy for recurrence of cardiac sarcoidosis on transplanted heart showing low tracer uptake findings at the inferior vena cava and anterior basal to the left ventricle, reduced in extent and gradient from previous, minimal residual active disease.

Table 2. Spirometric data of our patient at time 0, i.e. at the time of relapse on heart transplant, and at time 3 and time 6, i.e. 3 and 6 months after the start of therapy, respectively. At time 0 and time 6, only simple spirometry was performed, so data on residual volume and total lung capacity are not available

	Lower Limit of Normality	**Spirometry at T_0**	**Spirometry at T_3**	**Spirometry at T_6**
FEV_1	4,40 Lt	3,52 Lt (80%)	3,35 Lt (76%)	3,38 Lt (77%)
FVC	5,62 Lt	5,28 Lt (94%)	5,18 Lt (92%)	5,32 Lt (94%)
FEV1/FVC	78,78	66,66	64,63	63,53
RV	1,19 Lt	Not available	1,58 Lt (130%)	Not available
TLC	8,47 Lt	Not available	7,11 Lt (83%)	Not available
DLCO		70%	74%	89%
KCO		85%	91%	95%

Abbreviations: FEV_1: Forced expiratory volume, FVC: Forced vital capacity, RV: Residual volume, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, KCO: Krogh's k_{CO}.

studies, and 7 narrative reviews. Post-transplant CS recurrence was reported in less than 10% of patients, with a time interval ranging from 6 months to several years post-transplant. The diagnosis was mainly based on advanced imaging techniques, particularly PET-CT and CMR, often combined with endomyocardial biopsies to increase their diagnostic sensitivity, especially in cases of atypical presentation or doubtful diagnosis (10, 14, 16). Studies such as those conducted by Seplowe et al. (11, 13, 14) emphasized the importance of these techniques for timely and accurate diagnosis. The treatments described included the intensification of immunosuppression with high-dose corticosteroids, methotrexate, or mycophenolate mofetil, alone or in combination. These approaches showed clinical improvements in approximately 70% of the analyzed cases, with a reduction in granulomatous activity and stabilization of cardiac function, as demonstrated by serial imaging studies and cardiac function data. However, side effects related to immunosuppression were frequent, including opportunistic infections, liver toxicity, and metabolic disorders, which required careful clinical and laboratory monitoring (9, 10, 12, 21-24). In more complex cases refractory to standard treatments, a combination of therapies was observed, including calcineurin inhibitors (e.g., tacrolimus, cyclosporine) and biological drugs such as TNF-alpha inhibitors (13, 26), with variable results. Studies have also highlighted the role of methotrexate in the treatment of recurrent CS, especially in patients refractory to corticosteroids (10, 12, 27-29). Rezvani et al. (21) showed that PET-CT can be used to monitor methotrexate therapy. The analyzed case report confirmed a recurrence diagnosed by PET-CT and endomyocardial biopsy, treated with a combination of prednisone and methotrexate. After six months of treatment, a significant reduction in inflammation was observed, documented by the reduction in FDG uptake on PET-CT, and an improvement in the ejection fraction (EF) from 35% to 50%, as measured by echocardiography. The results obtained are consistent with the evidence of Bobbio et al. (18, 19), which emphasizes the importance of regular screening for the early detection of recurrences and of personalized therapies to optimize clinical outcomes. Furthermore, the analysis highlighted how the combined use of advanced imaging and biomarkers, such as sIL-2R, can improve the ability to monitor treatment response, minimizing complications. The review underscores the importance of standardized protocols for the diagnosis and treatment of recurrent CS and the need for further prospective studies to define the optimal role of immunosuppressive therapies, as reported in a case report by Rathore et al. (10, 29), highlighting the efficacy of methotrexate as first-line monotherapy.

Discussion

Post-transplant cardiac sarcoidosis recurrence represents a rare but clinically relevant condition, which requires a highly individualized and multidisciplinary approach (4, 10, 23). The data available in the literature are limited and mainly derived from case reports and small case series, making it difficult to establish standardized and robust evidence-based therapeutic protocols (Table 3). However, emerging

Table 3. Individual post-OHT recurrent cardiac sarcoidosis Studies

Study	Type	Age/ Gender	CS Diagnosis	OHT Diagnosis	Post-OHT Immuno.	Time to Recurrence	Presentation	Cell. Rej.	Recurrence Diagnostic	Recurrence Treatment	Outcome
Seplowe, 2024 (11)	Case Rep	46F	Pre-OHT	Dilated CM	Tacrolimus, Pred, MMF	2 wks	-	-	CMR	-	-
Sedaghat-Hamedani, 2019 (9)	Case Rep	43M	Post-OHT	ARVC	Methylpred, Myco, Tac	12 yrs	Symptomatic	-	FDG-PET CT	Adjusted	R: Declined, Anti-arrhythmic
Dotare, 2022 (26)	Case Rep	65M	Pre-OHT	-	Corticosteroids	1 yr	Symptomatic	-	18F-FDG PET	Methotrexate	R: Resolved
Rathore, 2024 (29)	Case Rep	31M	Pre-OHT	-	Methotrexate	1 yr	Symptomatic	-	18F-FDG PET	Methotrexate	R: Resolved
Khan, 2024 (12)	Case Rep	43F	Post-OHT	-	Tacrolimus, Pred, MMF	2 wks	-	-	EMB	High-dose MMF, Pred Pulse	-
Pandya, 2021 (16)	Survey	Variable	Pre-OHT	Post-OHT	Immunosuppression	Variable	-	-	-	Steroids	-
Inglis, 2023 (14)	Case Series	Variable	Pre-OHT	-	Tacrolimus, MMF, Pred	5 yrs (mean)	Symptomatic	+	EMB	Prednisone	R: Resolved
Rezvani, 2019 (21)	Case Rep	60+	Pre-OHT	-	-	1 yr	-	-	FDG PET	Methotrexate	-
Yager, 2005 (35)	Case Rep	26M	Post-OHT	-	Daclizumab, Myco, Tac	19 mos	Surveillance	+	EMB	Prednisone	R: Resolved
Ai-Ani, 2021 (17)	CR	59F	Post-OHT	Post-	Steroids, FK, MMF	5 yrs	Symptomatic	0	CMR	↑ Steroids, FK, MMF	R: Improved, LV Dysf
Schmidt, 2021 (36)	Retro-case	44	Post-OHT	Post-	Steroids, FK, EVE	11 mos	Symptomatic	0	EMB	Steroids	R: Resolved
Wiltshire, 2021 (37)	CR	43M	Post-OHT	Post-	Steroids, FK, MMF	11 mos	Symptomatic	0	EMB	↑ Steroids	R: Resolved
Sedaghat-Hamedani, 2020 (38)	CR	60M	Post-OHT	None	Steroids, FK, MMF	12 yrs	Symptomatic	0	FDG-PET CT	Adjusted	R: Resolved, Anti-arrhythmic
Blankstein, 2014 (39)	CR	50M	Pre-OHT	Pro-	Steroids, CSA, MMF	<3 yrs	Symptomatic	0	EMB	↑ Steroids	R: Resolved

Abbreviations: Study Type: Type of Study. Case Rep = Case Report, CR = Case Series/Retrospective Case Review, Retro-case = Retrospective Case Review, Survey = Survey, Case Series = Case Series, Retro-case = Retrospective Case Review. Disease: Underlying Disease. CS = Cardiac Sarcoidosis, GCM = Giant Cell Myocarditis, ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy. OHT Diagnosis: Underlying Cardiac Diagnosis for Orthotopic Heart Transplant. Post-OHT = Post-Orthotopic Heart Transplant (Recurrence after OHT), Pre-OHT = Pre-Orthotopic Heart Transplant (Recurrence in native heart before OHT), Dilated CM = Dilated Cardiomyopathy, ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy, None = No specific underlying cardiac diagnosis mentioned, Pro- = Probable Cardiac Sarcoidosis. Immuno.: Immunosuppression. Pre-OHT Immuno. = Pre-Orthotopic Heart Transplant Immunosuppression, Post-OHT Immuno. = Post-Orthotopic Heart Transplant Immunosuppression. MCS: Mechanical Circulatory Support. MCS Used: + = Yes, 0 = No. Cell. Rej.: Cellular Rejection. Cellular Rejection: + = Present, - = Absent, 0 = Not assessed/reported. Diagnosis: Recurrence Diagnostic Modality. EMB = Endomyocardial Biopsy, FDG-PET CT = Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography, 18F-FDG PET = 18F-Fluorodeoxyglucose Positron Emission Tomography, CMR = Cardiac Magnetic Resonance, IneF = Information not found. Treatment: Recurrence Treatment. Adjusted = Immunosuppression adjusted, Pred Pulse = Prednisone Pulse therapy, ↑ = Increased dose, +ATG, RTX = Antithymocyte Globulin and Rituximab. Outcome: Clinical Outcome. R = Recurrence, Resolved = Recurrence resolved, Declined = Clinical decline, Improved = Clinical improvement, LV Dysf = Left Ventricular Dysfunction, Anti-arrhythmic = Continued anti-arrhythmic therapy, UTI = Urinary Tract Infection. Medications (Abbreviated): Steroids = Corticosteroids, CSA = Cyclosporine A, AZA = Azathioprine, ATG = Antithymocyte Globulin, MTX = Methotrexate, MMF = Mycophenolate Mofetil, Tac = Tacrolimus, Pred = Prednisone, Methylpred = Methylprednisolone, FK = Tacrolimus (FK506), EVE = Everolimus, RTX = Rituximab.

evidence underscores the importance of immunosuppressive therapies in the management of these recurrences, with a key role for corticosteroids and agents such as methotrexate or mycophenolate mofetil, as illustrated by several studies (12, 10, 27-30). Previous studies have described cases of recurrence with a variable prevalence between 5% and 18% in patients transplanted for CS (7), with a variable time interval between 6 months and several years after transplantation, although cases of early recurrence have also been reported (11, 10). Diagnosis has often been complex (28, 16), with advanced imaging such as PET-CT and CMR used to detect granulomatous activity, while endomyocardial biopsies have proven essential for histological confirmation, even if with their limited sensitivity (10, 14, 16, 17). Haanschoten et al. (31) suggest that 3D mapping-guided endomyocardial biopsies may improve diagnostic yield. Immunosuppressive therapy, based on corticosteroids and agents such as methotrexate or mycophenolate, has shown variable results, highlighting the need for optimized protocols (23). Our case illustrates how the use of methotrexate, associated with corticosteroids, led to a significant clinical and functional improvement, with a reduction in symptoms, improvement in contractile function of the left ventricle, and reduction in tracer uptake on PET-CT. PET-CT has proven to be a crucial tool not only for diagnosis but also for monitoring treatment response, identifying areas of granulomatous activity that may not be detected with other diagnostic modalities, as evidenced by studies by Dotare et al. (10, 26), which support the utility of PET-CT for therapeutic monitoring (16, 22, 31). These results are consistent with the observations of Bobbio et al. (5, 18, 19), who have emphasized the importance of regular screening in patients transplanted for CS, and with evidence of the effectiveness of methotrexate as a second-line treatment, or even first-line, in cases of poor response to corticosteroids (10, 12, 27-30). The efficacy of methotrexate in combination with cyclosporine and prednisone suggests that these therapies may be considered cornerstones in the management of post-transplant CS recurrence. However, the risk of side effects related to immunosuppression, such as opportunistic infections, organ dysfunction, and metabolic disorders, requires careful and continuous monitoring of patients, as recommended by several studies (9, 10, 12, 21, 24, 32-37). Some authors have proposed the use of long-term therapies with reduced doses of steroids to prevent further recurrences (26). A multidisciplinary approach is essential, involving specialists in cardiology, pulmonology, radiology, and immunology, to address diagnostic and therapeutic complexities, as emphasized in several studies that report the importance of a team-based approach (10, 38-48). Furthermore, the adoption of advanced technologies, such as cardiac magnetic resonance and PET-CT, has the potential to significantly improve the ability to detect and manage these recurrences, allowing for personalized therapy and reducing the risk of adverse events related to disease reactivation. Crucially, the evidence of active myocardial inflammation on FDG-PET in conjunction with tachyarrhythmias was not immediately interpreted as CS recurrence. In retrospect, a more proactive multidisciplinary review at that stage could potentially lead to earlier diagnosis and treatment initiation, potentially improving outcomes. The management of heart transplant recipients is heavily focused on preventing organ rejection through a standardized immunosuppressive regimen. Typically, this includes induction therapy followed by maintenance immunosuppression with corticosteroids, calcineurin inhibitors (like tacrolimus or cyclosporine), and antimetabolites (like mycophenolate mofetil). These medications are crucial for preventing acute and chronic rejection, which are major causes of graft failure and mortality post-transplant. Routine endomyocardial biopsies are a cornerstone of post-transplant care, performed at scheduled intervals and in cases of suspected rejection, to monitor for cellular and antibody-mediated rejection. However, this immunosuppression, while necessary for graft survival, may not always be sufficient to prevent CS recurrence and, in some scenarios, could potentially contribute to a dysregulated immune environment. Cessation or significant reduction of immunosuppression, particularly mycophenolate and tacrolimus, to manage CS recurrence carries a substantial risk of allograft rejection a critical consideration in these patients. Therefore, a multidisciplinary approach involving transplant cardiologists, heart failure specialists, pulmonologists, and radiologists is paramount. This team needs to carefully weigh the risks and benefits of adjusting immunosuppression, considering both the potential for CS recurrence and the ever-present threat of organ rejection. The diagnostic challenge lies in differentiating CS recurrence from acute rejection, as both can present with myocardial inflammation

and dysfunction. Advanced imaging and sometimes repeat biopsies are crucial in this differential diagnosis. Further prospective studies are needed to better define the role of immunosuppressive therapies in recurrent cardiac sarcoidosis, with particular attention to the identification of more effective and safe therapeutic strategies. These studies could provide a basis for developing more robust guidelines and improving clinical outcomes in transplanted patients. There is growing interest in new therapeutic options, such as biological therapies, which may offer new opportunities for the treatment of CS refractory to conventional treatments (23, 26).

Conclusion

The purpose of this review is to make a significant contribution to the understanding of the management of recurrent cardiac sarcoidosis post-transplantation. Our research emphasizes that, despite the rarity of the condition, recurrences represent a clinical challenge that requires a targeted and personalized therapeutic approach. Advanced imaging, particularly PET-CT and CMR, and intensified pharmacological therapies based on corticosteroids and immunosuppressants such as methotrexate are essential tools to improve clinical outcomes and monitor the response to treatment. Although current evidence is limited, the reported data reinforce the need for further research aimed at optimizing treatment strategies and identifying biomarkers that can better predict recurrences. Furthermore, the introduction of standardized guidelines based on prospective studies and real-world data could optimize the treatment of this rare but complex pathology, ensuring a better long-term prognosis for patients.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: Conceptualization: A.S., R.C., B.R., L.M., F.S., and P.C.; Methodology: A.S., C.N., B.R., and N.R.; Software: N.R., C.T., and C.A.; Formal analysis: A.S., B.R., C.T., and M.H.; Investigation: A.S., B.R., C.T., and M.C.; Resources: M.C. and B.R.; Data curation: F.S. and P.C.; Writing – original draft: A.S., B.R., R.C., and M.H.; Writing – review and editing: A.S., B.R., L.M., M.C., and M.H.; Visualization: L.M. and R.C.

References

1. Kim JS, Judson MA, Donnino R, et al. Cardiac sarcoidosis. Am Heart J. 2009;157:9-21.
2. Li Y, Liang Z, Zheng Y, Qiao J, Wang P. Pulmonary sarcoidosis: from clinical features to pathology–a narrative review. Ann Palliat Med. 2021;10:9976-89.
3. Sonaglioni A, Fagiani V, Rigoni M, et al. Echocardiographic evaluation of left ventricular mechanics in sarcoidosis patients without overt heart disease: a systematic review and meta-analysis. Sarcoidosis Vasc Diffuse Lung Dis. 2024;41:e2024042.
4. Donsky AS, Escobar J, Capehart J, Roberts WC. Heart transplantation for undiagnosed cardiac sarcoidosis. Am J Cardiol. 2002;90:95-7.
5. Bobbio E, Björkenstam M, Nwaru BI, Jansson KA, Lund LH. Short and long-term outcomes after heart transplantation in cardiac sarcoidosis and giant cell myocarditis: a systematic review and meta-analysis. Clin Res Cardiol. 2022;111:125-40.
6. Markatis A, Papadopoulos N, Sarafidis P. Cardiac sarcoidosis: state-of-the-art review. Hippokratia. 2023;27:249.
7. Trivieri MG, Spagnolo P, Birnie DH, et al. Challenges in cardiac and pulmonary sarcoidosis: JACC state-of-the-art review. J Am Coll Cardiol. 2020;75:1017-35.
8. Kouranos I, Sharma R. Cardiac sarcoidosis: state-of-the-art review. Eur J Heart Fail. 2017;19:183-95.
9. Sedaghat-Hamedani F, Kayvanpour E, Hamed S, et al. The chameleon of cardiology: cardiac sarcoidosis before and after heart transplantation. ESC Heart Fail. 2019;6:1310-17.
10. Sharma A, Singh A, Pinney S. Management of cardiac sarcoidosis. J Thorac Dis. 2019;11(Suppl 10):S1313-19.
11. Seplowe M, Khan S, Vemulakonda L, et al. Probable recurrence of cardiac sarcoidosis in a transplanted heart. J Heart Lung Transplant. 2024;43:100146.
12. Khan SP, Seplowe M, Vemulakonda L, et al. Early recurrence of cardiac sarcoidosis after orthotopic heart transplantation. J Heart Lung Transplant. 2024;43:100146.
13. Jackson KC, Youmans QR, Wu T, et al. Cardiac transplant outcomes in cardiac sarcoidosis. J Heart Lung Transplant. 2022;41:113-22.
14. Inglis T, Lee J. Case series: recurrence of cardiac sarcoidosis after orthotopic heart transplantation. Transplant Direct. 2023;9:e1521.
15. Tanabe S, Nakano Y, Ando H, et al. Utility of new FDG-PET/CT guidelines for diagnosing cardiac sarcoidosis in patients with implanted cardiac pacemakers for atrioventricular block. Sci Rep. 2024;14:7825.
16. Pandya K, Sharma A, Birnie D. Management of cardiac sarcoidosis post heart transplantation: survey of transplant centers. Transplant Direct. 2021;7:e790.
17. Ai-Ani M, Taha MB, Stewart BD, et al. Cardiac sarcoidosis in the donor heart without extracardiac manifestations. BMJ Case Rep. 2021;14:e241902.
18. Oni AA, Hershberger RE, Norman DJ, Hunt SA, Schroeder JS. Recurrence of sarcoidosis in a cardiac allograft: control with augmented corticosteroids. J Heart Lung Transplant. 1992;11:367-9.
19. Perkel D, Czer LSC, Morrissey RP, et al. Heart transplantation for end-stage heart failure due to cardiac sarcoidosis. Transplant Proc. 2013;45:2384-6.
20. Akashi H, Kato TS, Takayama H, et al. Outcome of patients with cardiac sarcoidosis undergoing heart transplantation: a retrospective single-center analysis. J Cardiol. 2012;60:407-10.
21. Rezvani A, Rhee E, Khattak M, et al. Monitoring of methotrexate therapy of cardiac sarcoidosis with FDG PET: a case report. J Nucl Cardiol. 2019;26:1412-5.
22. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis-state of the art review. Cardiovasc Diagn Ther. 2016;6(1):50-63.
23. Matuszewski-Boros M, Kouranos I, Sharma R. Cardiac sarcoidosis treatment revisited. Curr Opin Cardiol. 2023;38:347-56.

24. Sato T, Aikawa T. Methotrexate for cardiac sarcoidosis: is it justifiable? Heart Fail Rev. 2021;26:91-8.
25. Vender RJ, Aldahham H, Gupta R. The role of PET in the management of sarcoidosis. Curr Opin Pulm Med. 2022;28:485-91.
26. Dotare T, Maeda D, Matsue Y, Minamino T. Effectiveness of methotrexate as a second-line treatment for cardiac sarcoidosis assessed via ^{18}F-FDG PET: a case report. Eur Heart J Case Rep. 2022;6:ytac217.
27. Vereecke E, Papageorgiou A, Kouranos I, Sharma R. Cardiac sarcoidosis: diagnosis and management. Expert Rev Cardiovasc Ther. 2022;20:793-808.
28. Sharma A, Birnie D. Management of cardiac sarcoidosis. Can J Cardiol. 2017;33:1184-95.
29. Rathore A, Zaidi SF, Kronen T, Hanna D, Kaur IP, Kaeley G. Efficacy of methotrexate as first-line monotherapy for cardiac sarcoidosis evaluated via ^{18}F-FDG PET scans one year apart: a case report. Am J Respir Crit Care Med. 2024;209:A4008.
30. Haanschoten DM, Adiyaman A, 't Hart NA, Jager PL, Elvan A. Value of 3D mapping-guided endomyocardial biopsy in cardiac sarcoidosis: case series and narrative review on the value of electro-anatomic mapping-guided endomyocardial biopsies. Eur J Clin Invest. 2021;51: e13497.
31. Burke WM, Keogh A, Maloney PJ, Delprado W, Bryant DH, Spratt P. Transmission of sarcoidosis via cardiac transplantation. Lancet. 1990;336(8730):1579.
32. Torregiani C, Reale M, Confalonieri M, et al. Cardiopulmonary exercise testing complements both spirometry and nuclear imaging for assessing sarcoidosis stage and for monitoring disease activity. Sarcoidosis Vasc Diffuse Lung Dis. 2024;41:e2024017.
33. Pozzan R, Salton F, Confalonieri P, et al. Autoantibodies in sarcoidosis: innocent bystander or promising biomarker for organ involvement? Sarcoidosis Vasc Diffuse Lung Dis. 2024 Dec 10;41:e2024056.
34. Bardakci MI, Ayhan Albayrak G. Quality of life, fatigue and markers in sarcoidosis: a section from Turkey. Sarcoidosis Vasc Diffuse Lung Dis. 2024;41:e2024049.
35. Yager JE, Hernandez AF, Steenbergen C, et al. Recurrence of cardiac sarcoidosis in a heart transplant recipient. J Heart Lung Transplant. 2005;24(11):1988-90. doi: 10.1016/j.healun.2005.02.016
36. Schmidt TJ, Rosenbaum AN, Kolluri N, et al. Natural history of patients diagnosed with cardiac sarcoidosis at left ventricular assist device implantation or cardiac transplantation. ASAIO J. 2021;67:583-7.
37. Wiltshire S, Nadel J, Meredith T, et al. Twice bitten, thrice shy: a case of recurrent isolated cardiac sarcoidosis in the transplanted heart. JACC Case Rep. 2021;3(3):427-32.
38. Sedaghat-Hamedani F, Kayvanpour E, Hamed S, et al. The chameleon of cardiology: cardiac sarcoidosis before and after heart transplantation. ESC Heart Fail. 2020;7:692-6.
39. Blankstein R, Osborne M, Naya M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol. 2014;63: 329-36.
40. Toscano G, Tartaro P, Fedrigo M, Angelini A, Marcolongo R. Rituximab in recurrent idiopathic giant cell myocarditis after heart transplantation: a potential therapeutic approach. Transpl Int. 2014; 27:e38-42.
41. Vaidya GN, Czer LSC, Luthringer D, et al. Heart transplantation for giant cell myocarditis: a case series. Transplant Proc. 2021;53: 348-52.
42. Patel PM, Saxena A, Wood CT, et al. Outcomes of mechanical circulatory support for giant cell myocarditis: a systematic review. J Clin Med. 2020;9:3905.
43. Cifaldi R, Salton F, Confalonieri P, et al. Pulmonary sarcoidosis and immune dysregulation: a pilot study on possible correlation. Diagnostics (Basel). 2023;13:2899.
44. Chianese M, Screm G, Confalonieri P, et al. Nailfold videocapillaroscopy in sarcoidosis: new perspectives and challenges. Tomography. 2024;10:1547-63.
45. Vermeer B, Veltkamp M, Raasing LRM, Wind AE, Vorselaars ADM. Hydroxychloroquine monotherapy in sarcoidosis: indications, efficacy, and side effects. Sarcoidosis Vasc Diffuse Lung Dis. 2024;41(3): e2024039.
46. Hughes M, Bruni C, Cuomo G, et al. The role of ultrasound in systemic sclerosis: on the cutting edge to foster clinical and research advancement. J Scleroderma Relat Disord. 2021;6(2):123-32.
47. Ruaro B, Pozzan R, Confalonieri P, et al. Gastroesophageal Reflux Disease in Idiopathic Pulmonary Fibrosis: Viewer or Actor? To Treat or Not to Treat? Pharmaceuticals (Basel). 2022;15(8):1033.
48. Raasing L, Veltkamp M, Datema M, Korenromp I, Grutters JC, Vogels OJM. Sarcoidosis-related small fiber neuropathy: focus on fatigue, pain, restless legs syndrome, and cognitive function. Sarcoidosis Vasc Diffuse Lung Dis. 2025;42:16214.