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CLINICAL CASE SERIES

Multisystemic, Possibly Familial Sarcoidosis Ameliorated by an mTOR Inhibitor

Roxxy Brown, BSc,[a] Sharon Macrohon-Sabaitue, ANP/CNP,[b] Mark Specterman, MD, PhD,[c] Angeliki Asimaki, PhD[c]

ABSTRACT

BACKGROUND Sarcoidosis is an inflammatory, multisystemic, potentially life-threatening disease with a precise etiology that remains largely unknown. It is characterized by granuloma formation in various organs that can lead to permanent organ scarring and failure. Currently there is no curative treatment. Traditional drug interventions target reduction of inflammation and symptom control and have not shown definitive proof of a survival benefit.

CASE SUMMARY We present the cases of a mother and son treated for chronic aggressive multiorgan sarcoidosis with sirolimus, a mammalian target of rapamycin (mTOR) inhibitor. Both patients experienced a marked reversal of inflammation in their respective affected organs coupled with profound symptom relief.

CONCLUSIONS Inhibition of mTOR may be an effective, safe treatment option for patients with conventional-drug-resistant forms of systemic sarcoidosis. (JACC Case Rep. 2025;30:103633) © 2025 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/).

Sarcoidosis is a systemic inflammatory disease involving aberrant cytokine activation that results in epithelioid cell clustering and the formation of non-necrotizing granuloma, which in turn can potentially lead to organ scarring and dysfunction.[1] The etiology of the disease has yet to be elucidated.[1] Historically, sarcoidosis was believed to be environmentally triggered.[2] However, recent studies have shown a strong genetic component: patients who have a direct relative affected exhibit a 3.7-fold rise in disease susceptibility.[2]

TAKE-HOME MESSAGES

- Sarcoidosis is a potentially fatal disease, but current management options primarily (and not necessarily effectively) target the symptoms.
- This report shows mTOR inhibition may be a mechanism-based, potentially effective approach for patients with aggressive, systemic sarcoidosis that does not respond to conventional therapies.

From [a]Strate Medical Research, North Miami, Florida, USA; [b]Primary Medical Physicians, Zenith Clinical Research, Memorial Hospital System, Hollywood, Florida, USA; and the [c]Cardiovascular and Genomics Research Institute, School of Health & Medical Sciences, City St. George's, University of London, London, United Kingdom.

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ABBREVIATIONS AND ACRONYMS

CS = cardiac sarcoidosis

CT = computed tomography

EF = ejection fraction

FDG-PET = fludeoxyglucose-18 positron emission tomography

HF = heart failure

LV = left ventricular

MRI = magnetic resonance imaging

mTOR = mammalian target of rapamycin

The diagnosis of sarcoidosis is traditionally based on 3 major criteria: a compatible clinical presentation, identification of non-necrotizing granulomatous inflammation in 1 or more tissue samples, and exclusion of alternative causes of granulomatous disease. Although progress has been made in establishing universally accepted measures to determine whether each diagnostic criterion has been satisfied, this condition in a large number of affected individuals remains undiagnosed.[3-5] Although only ~5% of patients with sarcoidosis have clinically manifest cardiac involvement, the prevalence of cardiac sarcoidosis (CS) in autopsy series lies between 25% and 50%.[6] The most significant complications of manifest CS are conduction abnormalities, atrial and ventricular arrhythmias, heart failure (HF), and sudden cardiac death.[6]

Corticosteroids are the first-line immunosuppressive agents for CS. However, early initiation of second-line steroid-sparing medications has been advocated, and there are data suggesting that concomitant initiation of therapies may be more beneficial. The efficiency of third-line anti-tumor necrosis factor agents (such as infliximab and adalimumab) remains controversial.

Management of CS is particularly challenging because early cardiac involvement is often missed and the condition is only diagnosed in a large subset of patients at their time of presentation with HF or arrhythmic complications.[7] Patients with systemic sarcoidosis and CS have a worse prognosis than patients without cardiac involvement. A history of sustained ventricular tachycardia, an increased left ventricular (LV) end-diastolic diameter, and an increased NYHA functional class are independent predictors of mortality in CS patients.[8] HF as a clinical manifestation and reduced LV ejection fraction (EF) carry an especially poor prognosis, with a reported 10-year survival of 19% to 53% without a cardiac transplant.[8]

In light of these factors, there is now a pivotal need to shift from symptom targeting to precision, mechanism-based interventions. We present a familial case series in keeping with aggressive multiorgan sarcoidosis with a positive response to mammalian target of rapamycin (mTOR) inhibition.

CASE REPORT

Patient 1 is currently a 51-year-old man in the United States who presented at 42 years of age with diarrhea, rectal bleeding, a distended abdomen, and symptoms of dizziness. Computed tomography (CT), X-ray, and magnetic resonance imaging (MRI) investigations were inconclusive for causation, but the patient was given a diagnosis of idiopathic inflammatory bowel disease. He was prescribed antibiotics and a short course of prednisolone, which did not improve his symptoms.

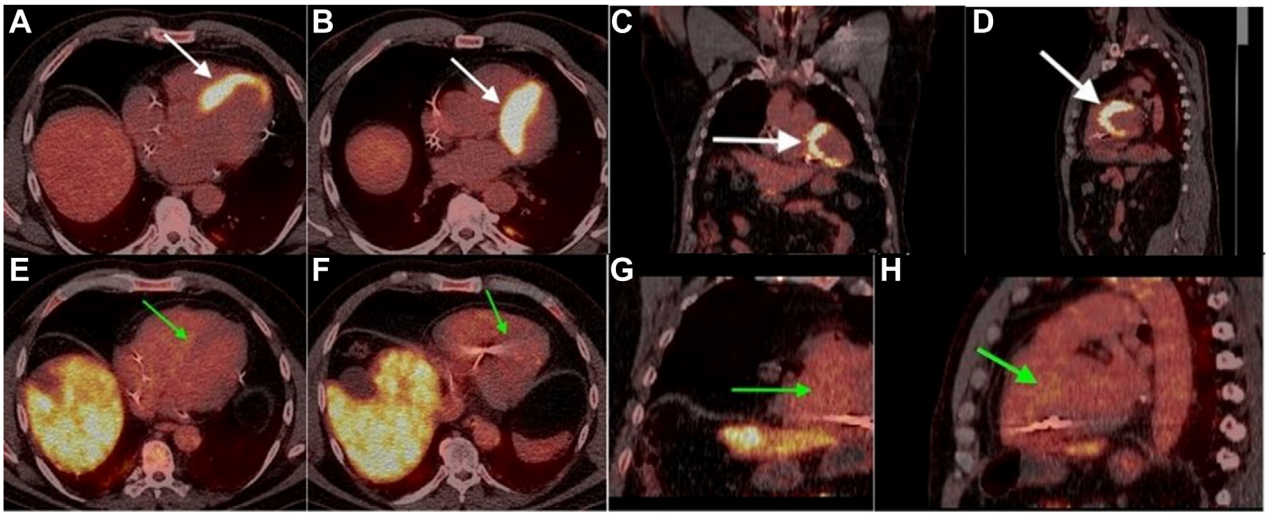
When he was 47 years old, the patient was assessed by a dermatologist and found to have excoriated erythematous papules on the left posterior scalp as well as on the left preauricular area. Although lupus pernio was not diagnosed at the time, the consultant dermatologist noted that the lesions were highly reminiscent of those seen in patients with sarcoidosis. A year later, the patient presented with symptoms and signs of HF (LVEF = 40%), increasing pulmonary distress, allergy-induced asthma, and sinusitis. He had no history of smoking or any unusual environmental exposure. He was prescribed albuterol inhalers, and a cardiac MRI was ordered.

The MRI findings included diffuse LV and right ventricular hypokinesis with relative akinesis within the anteroseptal wall. There were segmental areas of diminished perfusion, several heterogenous foci of delayed gadolinium enhancement (most prominent within the LV basal septal wall), myocardial edema, and associated myocardial thickening. The contrast enhancement was nonischemic in pattern. Lung and lymph node biopsy samples obtained shortly afterward excluded an infectious process but were positive for non-necrotizing granulomas, and the patient was reclassified with a diagnosis of sarcoidosis with cardiac involvement.

The patient was put on methylprednisolone (starting dose: 20 mg daily). methotrexate (starting dose: 15 mg/week), and folic acid (500 mg daily). Several attempts were made to taper the methylprednisolone dosage, all of them resulting in symptom flare-ups. After each such flare-up, the dosage was increased to 60 mg daily; further attempts to taper to 20 mg at different rates were made. Methotrexate was increased to 20 mg/week but caused significant side effects, including extreme fatigue, lethargy, brain fog, vomiting, dizziness, joint pain, blurry vision, and headaches. A different folate supplement (Rheumate; Primus Pharmaceuticals) was added to the regimen with no resolution of the methotrexate-related side effects. Accordingly, the patient could not tolerate an increase to the recommended 25 mg/week dosage.

With no symptom resolution, a skull base to mid-thigh fludeoxyglucose-18 positron emission tomography (FDG-PET) scan was performed 6 months after diagnosis and therapy initiation. The scan showed an

FIGURE 1 Representative FDG-PET Images From Patient 1



(A to D) Fludeoxyglucose-18 positron emission tomography (FDG-PET) images before mammalian target of rapamycin (mTOR) inhibitor therapy and (E to H) after mTOR inhibitor therapy. Pretreatment images showing (A and B) 2 sequential axial slices, (C) coronal and (D) sagittal views, respectively, demonstrate severe FDG-avid uptake along the basal and midanterior, septal and inferior left ventricular wall with moderate uptake extending to the apical septal wall (white arrows). Posttreatment images showing (E and F) 2 sequential axial slices, (G) coronal and (H) sagittal views, respectively, demonstrate near complete resolution of hypermetabolic uptake with trace FDG-avid uptake along the midseptal wall (green arrows). Of note, the increased FDG uptake in the liver was attributed to contemporary viral hepatitis.

indeterminate 2-cm focus of moderate tracer uptake in the distal stomach, moderate intensity cardiac uptake involving the basal, midanterior, anteroseptal, and inferoseptal segments as well as mild inferior segment intensity, and subcentimeter calcified mediastinal lymph nodes, all indicative of nonresponse to steroid/methotrexate therapy.

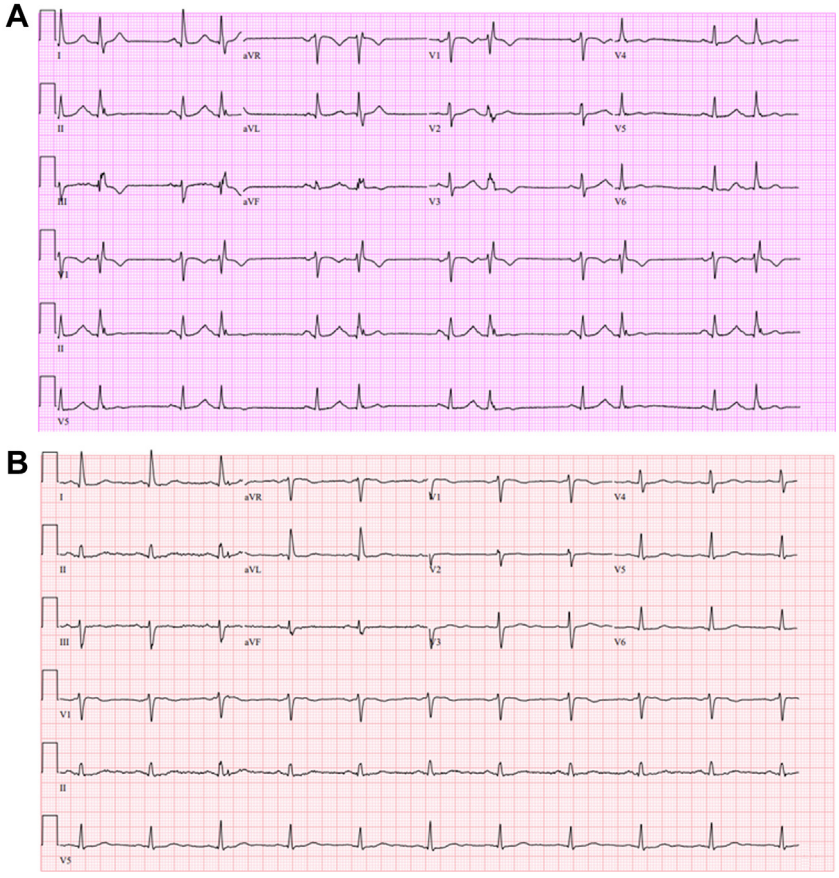
Infliximab-abda infusion was added to the patient's treatment plan. The patient's weight at the time was increased (136 kg) due to prednisone-related fluid retention. Accordingly, infliximab was first given at a dosage of 700 mg for 8 weeks (5 mg/kg). The dosage was subsequently increased to 800 mg for 8 weeks and finally to 800 mg for 6 weeks. Moreover, the patient was initiated on metoprolol at 200 mg daily, spironolactone at 25 mg daily, and sacubitril/valsartan at 49/51 mg twice daily (Entresto; Novartis).

A repeat FDG-PET scan was ordered 18 months later, which showed substantial progression of intensely hypermetabolic CS (**Figures 1A to 1D**). The patient was converted from infliximab/methotrexate to mycophenolate mofetil (500 mg twice daily), but this was discontinued after 30 days because of adverse side effects (gout). Due to the lack of drug response, the patient chose to discontinue all medications other than methylprednisone and albuterol.

Patient 2 is currently a 75-year-old woman being treated in the United States, and she is the biological mother of patient 1. She had a short history of occasional smoking until 1984, and to our knowledge she has never been exposed to any unusual environmental conditions. At age 50 she presented with breathing difficulty and was given a diagnosis of chronic obstructive pulmonary disease. She also suffered from chronic arthritis.

Patient 2 showed inflammatory skin lesions on her scalp and neck similar to those of patient 1. When she was 62 years old, she presented with atrial fibrillation and was started on dronedarone (400 mg twice daily) and later underwent an ablation. After ablation, the patient then presented with further arrhythmias—namely, nonsustained ventricular tachycardia, ventricular bigeminy, and atrial ectopics with aberrant conduction (**Figure 2A**). A cardiac MRI showed LV hypertrophy, mild/moderate biatrial enlargement, and enlarged caliber of the main pulmonary artery suggestive of pulmonary hypertension. There was no evidence of coronary artery disease. An X-ray performed in 2019 showed a nodule posteriorly at the right lung base, which appeared larger and sharply marginated in a follow-up X-ray in 2021. A CT scan performed in 2023 showed calcified mediastinal and

FIGURE 2 Representative ECGs From Patient 2



Electrocardiograms (ECGs) (A) before mTOR inhibitor therapy (2016) and (B) after mTOR inhibitor therapy (2024). Pretreatment ECG shows atrial ectopics with aberrant conduction. Posttreatment ECG shows normal sinus rhythm without any abnormalities. Abbreviation as in Figure 1.

hilar lymph nodes, calcified granulomas in the lungs, spleen, and liver, and several sub-6-mm noncalcified lung nodules along with a reduced pulmonary diffusion capacity (Figure 3A).

Based on these findings, her diagnosis was changed to idiopathic emphysema, and she was prescribed inhaled steroids. Patient 2's insurance plan did not cover a PET scan and lung biopsy. When multisystemic sarcoidosis was diagnosed in patient 1, patient 2 was reviewed again. With no alternative cause identified to explain the progressive nature of her cardiac and pulmonary manifestations, sarcoidosis was offered as a diagnosis of exclusion by her treating physicians. However, her disease activity was not regarded as severe enough to warrant systemic anti-inflammatory therapy.

In early 2024, owing to their deteriorating health and its profound effect on their quality of life, the patients and their relatives contacted the UK-based authors of this report for advice. This was prompted by the preclinical evidence the authors had presented on the beneficial effect of sirolimus in models of cardiac sarcoid.[9] These preclinical data, together with the available evidence of the benefits of sirolimus in different forms of sarcoid,[10-13] led to the patients initiating a trial of sirolimus, which was provided to them by practitioners in the United States. Patient 1 received 4 mg daily, and patient 2 received 2 mg daily. Of note, patient 1 discontinued methylprednisone 2 days before the initiation of sirolimus.

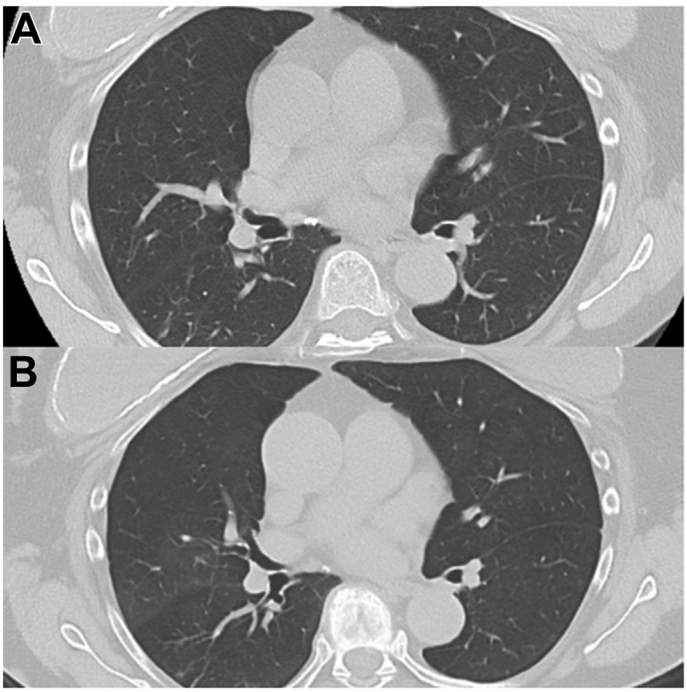
Within 1 month, patient 1 experienced a noticeable decrease in intestinal upset and bloating along with less labored breathing, which allowed for the discontinuation of albuterol. A repeat FDG-PET scan performed 3.5 months after therapy had been initiated revealed interval resolution of both cardiac and

pulmonary inflammation (Figures 1E to 1H). Additionally, the sinusitis of patient 1 resolved. As of the time of writing, patient 1 has normal cardiac function (EF = 60%) and is experiencing no discernible symptoms of sarcoidosis.

Within 1 month from sirolimus initiation, patient 2 experienced rapid improvement in her breathing difficulty, which allowed for discontinuation of her inhaled corticosteroids. There was also almost complete resolution of her chronic joint pain and inflammatory skin lesions. A repeat CT scan 3 months after therapy initiation showed lung nodule resolution (Figure 3B). One month later, patient 2's dosage was increased to 4 mg daily, which alleviated all her remaining joint pain within 2 weeks. At the time of writing, patient 2 is in sinus rhythm and shows no electrocardiographic abnormalities (Figure 2B).

Both patients experienced mild stomach upset that resolved by day 30 of treatment. Neither patient experienced any other adverse reactions, and their full blood count results remain within the normal range.

FIGURE 3 Representative Pulmonary Computed Tomography Scan Images From Patient 2



Pulmonary computed tomography scan images (A) before mTOR inhibitor therapy and (B) after mTOR inhibitor therapy. Pretreatment scan shows extensive nodules in the left upper and lower lobes, which are resolving after 3 months of sirolimus treatment. Abbreviation as in Figure 1.

DISCUSSION

Although a portion of sarcoidosis patients are asymptomatic, others experience severe health complications. Currently, the treatment options are not curative but rather primarily target the symptoms.[14,15] When pharmacologic intervention is required, the first-line treatment is often systemic corticosteroids. For patients with CS or those who cannot tolerate corticosteroids, concomitant therapy with other steroid-sparing agents (methotrexate, azathioprine, leflunomide, or mycophenolate) is generally recommended. For the patients who do not respond to first- and second-line options, tumor necrosis factor antagonists (infliximab or adalimumab) have been used with varied outcomes.[14,15]

At present, there are no randomized controlled trials that detail a superior treatment plan.[15] Long-term corticosteroid treatment is associated with a high risk of adverse effects and morbidity, and there is limited evidence to support that the second and third lines of treatment result in better patient outcomes.[14-16] For the patients described in this report, numerous drugs had been given with no measurable effect on the disease course. Sirolimus, however, halted and reversed disease progression within 3.5 months.

Sirolimus, also known as rapamycin, is a potent mTOR inhibitor that was approved by the U.S. Food and Drug Administration in 1999 for immunosuppression after organ transplantation and in 2015 for the treatment of lymphangioleiomyomatosis.[17] Studies on different patient cohorts have shown that chronic use of sirolimus is safe, well-tolerated, and associated mostly with mild adverse events.[17]

Cellular homeostasis is maintained by mTOR, an ubiquitous protein kinase.[17] The mTOR signaling cascade consists of 2 distinct multisubunit complexes named mTOR complex 1/2 (mTORC1/2). Sirolimus inhibits mTORC1 activity by forming a complex with FK506-binding protein 2 (FKBP2).[17] Aberrant mTOR activation has long been associated with several granulomatous and fibrotic diseases, including idiopathic pulmonary fibrosis.[17] Increased myocardial mTOR activity was seen in 78% of sudden cardiac death victims linked to CS.[9] Mutations in elements of the mTOR signaling pathway have been found in familial sarcoid cases, and murine models with a conditional deletion of the mTOR pathway tuberous sclerosis 2 (*TSC2*) gene exhibit cardiac granulomas highly reminiscent of CS in patients.[9,18]

Case studies have shown successful responses to sirolimus in laryngeal and pulmonary sarcoidosis

patients, and a clinical trial showed marked histologic improvement of skin lesions in 70% of patients with a cutaneous form of the disease.[10-12] Moreover, a recently published case series showed a marked reduction of myocardial inflammation in CS patients treated with an mTOR inhibitor.[13] However, to our knowledge, the efficacy of mTOR inhibition has not been tested in patients with uncontrolled systemic sarcoidosis.

The remarkable response to sirolimus presented herein needs to be replicated in larger-scale patient studies. Moreover, we acknowledge that the short-term therapy duration does not preclude the possibility of disease relapse in the future or the emergence of adverse side effects. Also, we need to highlight that mTOR is a ubiquitous protein involved in several physiological functions. Consequently, the mechanistic effects of its inhibition may be pleiotropic. Nevertheless, our study suggests that mTOR inhibition may be an effective, safe treatment option for patients with persistent, conventional-drug-resistant forms of systemic sarcoidosis.

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ADDRESS FOR CORRESPONDENCE: Dr Angeliki Asimaki, Cardiovascular and Genomics Research Institute, School of Health & Medical Sciences, City St George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. E-mail: aasimaki@sgul.ac.uk.

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KEY WORDS autoimmune, ejection fraction, ventricular tachycardia