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CASE REPORT

CLINICAL CASE

New-Onset Neurosarcoidosis Following Heart Transplant for Cardiac Sarcoidosis

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ABSTRACT

A 63-year-old woman who underwent heart transplantation for cardiac sarcoidosis developed new headache and vision changes. Extensive workup resulted in a diagnosis of neurosarcoidosis treated with pulse dose steroids and infliximab. Recurrence of sarcoidosis after transplantation for isolated cardiac sarcoidosis occurs, but optimal surveillance methods remain unknown. (J Am Coll Cardiol Case Rep 2024;29:102358) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 63-year-old woman who underwent orthotopic heart transplantation (OHT) for cardiac sarcoidosis (CS) was admitted 7 months later with severe vomiting, diarrhea, headache, vision changes, and cold intolerance. She had a 1-month history of watery stools and poor oral intake tolerance. She reported a new, pressure-like headache with transient vision changes in her right eye. Her vitals were notable for mild tachycardia and normotension. Her physical exam was notable for dry mucus membranes, soft nondistended abdomen, and nonfocal neurologic exam.

LEARNING OBJECTIVES

- To formulate the appropriate workup and management of sarcoidosis recurrence posttransplant.
- To recognize current outcomes and challenges of posttransplant care in patients with CS.

PAST MEDICAL HISTORY

The patient's history was notable for heart failure with reduced ejection fraction secondary to presumed CS following characteristic late gadolinium enhancement seen on cardiac magnetic resonance imaging (MRI). She had no known extracardiac sarcoidosis manifestations. She was started on guideline-directed medical therapy and prednisone at the time of diagnosis. She was hospitalized for refractory ventricular tachycardia requiring urgent evaluation for OHT. Pretransplant chest computed tomography scan showed no lymphadenopathy, and head computed tomography scan showed no acute abnormalities. Her posttransplant course was complicated by significant C4d staining, donor-specific antibodies, and new atrial flutter, requiring increased immunosuppression with mycophenolate mofetil from 1,000 mg twice daily to 1,500 mg twice

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ABBREVIATIONS AND ACRONYMS

CS = cardiac sarcoidosis

MRI = magnetic resonance imaging

OHT = orthotopic heart transplantation

PET = positron emission tomography

daily and a prolonged prednisone taper. Her explanted heart confirmed CS based on gross pathology and microscopy (Figures 1A to 1C).

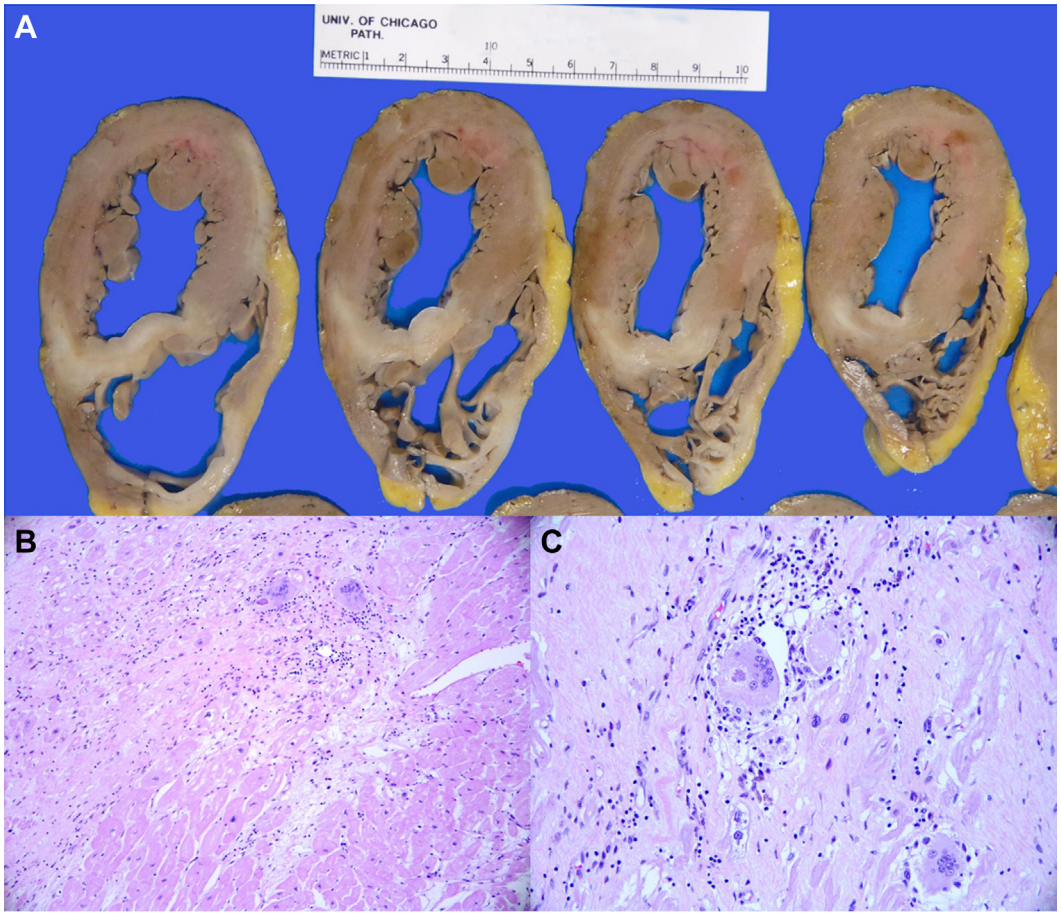
DIFFERENTIAL DIAGNOSIS

Differential diagnosis for her neurologic symptoms and headache included malignancy, infection, and new neurologic involvement of her prior sarcoidosis. Differential diagnosis for her diarrhea and vomiting included medication side effect and infection. Her cold intolerance was concerning for a new endocrine disorder.

INVESTIGATIONS

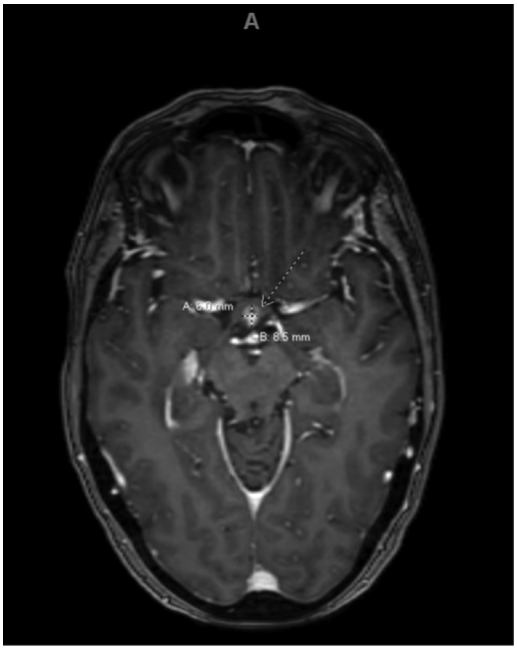
Serum labs were consistent with central hypothyroidism, diabetes insipidus, and central hypogonadism, raising the concern for a singular, central

FIGURE 1 Pathology Confirming Cardiac Sarcoidosis



(A) Gross pathology: Cross sections of the explanted heart show multiple areas of fibrosis involving both ventricles and interventricular septum consistent with cardiac sarcoidosis. (B) Photomicrograph of representative section from the left ventricle shows well-defined area of fibrosis with 2 multinucleated giant cells and few lymphocytes. An area of preserved myocytes can be seen in the lower right (hematoxylin-eosin stain; original magnification ×100). (C) Photomicrograph of another area showing fibrosis, multinucleated giant cells (one of which near the center contains an asteroid body in its cytoplasm) and entrapped myocytes (hematoxylin-eosin stain; original magnification ×200).

FIGURE 2 Brain Magnetic Resonance Imaging Demonstrating Discrete Enhancement Involving the Hypothalamus in the Midline With Mass Effect on the Adjacent Chiasm



process. Brain MRI showed discrete enhancement of the hypothalamus (Figure 2), with subsequent positron emission tomography (PET) scan demonstrating fluorodeoxyglucose-avid focus near the sella turcica. Infectious workup, including lumbar puncture, was negative, except for a noninvasive pathogen blood test (Karius Inc) positive for trichodysplasia spinulosa-associated polyomavirus. The infectious disease team determined this to be of low concern as a clinically significant infection. In addition, cerebrospinal fluid cytology was negative for malignancy. Unfortunately, the brain lesion itself was too deep to be safely biopsied. Separately, a colon biopsy demonstrated erosion with marked regenerative features consistent with mycophenolate toxicity as the etiology of her diarrhea.

MANAGEMENT

After extensive discussion with the infectious disease, neurology, neurosurgery, and rheumatology teams, and considering the negative infectious and malignancy results, the patient was given an empiric course of 1,000 mg daily intravenous methylprednisolone for 3 days, which improved her symptoms. The neurology team noted that her presentation was not consistent with multiple sclerosis or a demyelinating disease, and in the context of her confirmed sarcoidosis on explanted heart pathology, she fulfilled diagnostic criteria for presumed neurosarcoidosis.

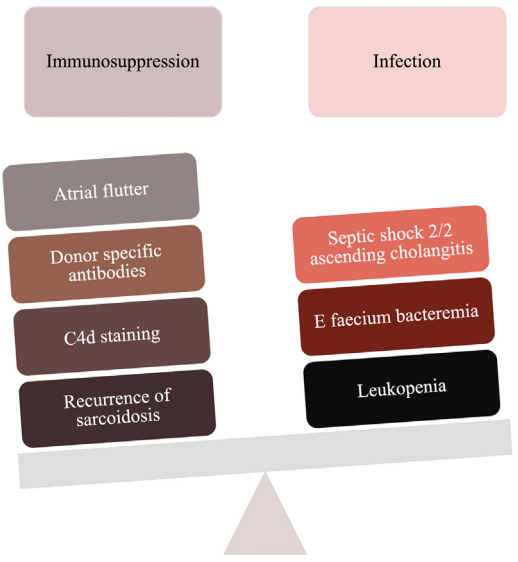
Given this new diagnosis and her concurrent diagnosis of mycophenolate toxicity, adjustments were made to her immunosuppression regimen. Mycophenolic acid was discontinued and everolimus was added to her post-transplant immunosuppression, along with continuation of her calcineurin inhibitor. She was transitioned to an oral prednisone taper starting at 60 mg daily tapering by 5 mg every 4 weeks. On transitioning to oral steroids, her symptoms recurred, so the rheumatology team recommended adding infliximab infusions every 6 weeks to her immunosuppressive regimen of tacrolimus (goal 4-6), everolimus (goal 3-5), and a prolonged prednisone taper.

DISCUSSION

Patients transplanted for CS have similar rates of infection, graft failure, and survival to those without sarcoidosis.[1] Systematic reviews of the literature report recurrence of sarcoidosis posttransplant ranges from 4% to 18%.[1-3] Risk factors and immunosuppressive regimen at time of recurrence are not well studied. Optimal immunosuppressive therapy for patients with sarcoidosis undergoing OHT is unknown, but in practice patients transplanted for CS tend to continue on glucocorticoids longer than those without sarcoidosis.[3]

The best method of evaluation of extracardiac sarcoidosis before transplantation is unknown. In one study, 91% of patients with presumed isolated CS were found to have extracardiac manifestations.[4] Whole-body PET to evaluate extracardiac manifestations may be indicated as part of an OHT evaluation, although differences in posttransplant immunosuppression and outcomes between patients with isolated CS and those with extracardiac sarcoidosis are not well understood.[5] Case studies demonstrate surveillance with cardiac MRI and PET in patients with CS can result in changes to immunosuppressive management before the development of clinical symptoms.[6,7] Optimal surveillance of recurrence of sarcoidosis posttransplant is not well studied, but cardiac MRI and fluorodeoxyglucose-PET surveillance

FIGURE 3 Balance of Rejection/Recurrence and Infection



has been proposed.[4,6] There is a definite need for additional research on optimal monitoring, immunosuppressive protocols, and recurrence management for patients undergoing heart transplant for CS.

To our knowledge, there is only 1 additional reported case of neurosarcoidosis post-OHT,[8] although this was only published in abstract form in 2002 and additional details are not known.[8] Neurosarcoidosis is reported to occur in 5% to 10% of patients with sarcoidosis and is associated with increased mortality.[9,10] Hypothalamic and pituitary involvement represents 10% to 25% of neurosarcoidosis cases.[9] Biopsy is the gold standard of diagnosis, but diagnostic criteria for probable neurosarcoidosis can be met with clinical manifestations, MRI findings, known systemic granulomatous disease, and rigorous exclusion of other potential etiologies of neurologic symptoms. Neurosarcoidosis is primarily treated with glucocorticoids, with the addition of mycophenolate, methotrexate, or infliximab in refractory cases.[9]

FOLLOW-UP

The patient improved and was discharged. One week after her second dose of infliximab, she was admitted with septic shock due to ascending cholangitis, requiring vasoactive support. She was started on broad-spectrum antibiotics and underwent endoscopic retrograde cholangiopancreatography. Despite these therapies, she became more hemodynamically unstable with multiorgan failure requiring extracorporeal membrane oxygenation. She did not improve clinically and was ultimately transitioned to comfort care and died. Her family declined autopsy, so pathology confirming neurosarcoidosis or sarcoidosis recurrence in her transplanted heart was not able to be obtained.

CONCLUSIONS

Further study is needed to understand if whole-body PET before OHT for CS would change management or outcomes. Furthermore, optimal methods of surveillance for posttransplant recrudescence of sarcoidosis have not been established but may include serial imaging with cardiac MRI and PET scans. Balancing adequate immunosuppression with infection risk posttransplant is further complicated in instances of sarcoidosis recurrence (**Figure 3**).

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KEY WORDS **cardiac sarcoidosis, heart transplant, neurosarcoidosis, posttransplant immunosuppression, sarcoidosis**