

CASE STUDY: CARDIAC SARCOIDOSIS RESOLVED WITH MYCOBACTERIUM AVIUM PARATUBERCULOSIS ANTIBIOTICS (MAP)

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ABSTRACT. *Background:* The author presents a clinical history and personal case study following his diagnosis of inactive sarcoidosis in 2004, followed by an acute episode of cardiac sarcoidosis (CS) in 2012 which resulted in complete heart block, cardiac myopathy, heart failure and insertion of an implantable cardioverter defibrillator (ICD) pacemaker. *Methods:* Following a detailed review of the clinical and scientific literature he concluded that sarcoidosis may be a mycobacterial infection and could be treated with anti-MAP antibiotic regime (1) developed to treat Crohn's disease. *Findings:* After successful culture and identification of viable MAP in his blood, treatment with the MAP antibiotic regime for one year led to complete metabolic resolution of the previously avid cardiac sarcoidosis and no PET evidence of any metabolically active sarcoidosis anywhere. Such reversal of cardiac sarcoidosis has never previously been reported. (*Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35: 171-177)

KEY WORDS: cardiac sarcoidosis, hypercalciuria, mycobacteria, MAP, antibiotics

INTRODUCTION

Sarcoidosis, first described more than 120 years ago, is a multisystem disease of unknown cause that is characterised by the formation of granulomas in various organs, mainly the lungs and the lymphatic system. Most patients present with pulmonary involvement characterized by hilar lymphadenopathy on chest x-ray (2) and about half are asymptomatic. Of patients with systemic sarcoidosis, 2-5% have CS, although autopsy studies and modern cardiac imaging suggests that this may represent only a small proportion of CS patients. CS may be manifested by silent myocardial granulomas, that can lead to

symptomatic conduction disturbances, ventricular arrhythmias and progressive heart failure and sudden death. In sarcoidosis localised only to the heart (3) detection may be delayed and the prognosis is poorer.

In clinical literature on the diagnosis and treatment of sarcoidosis (2-4), the aetiology of the disease is said to be unknown, and could involve infectious agents, non-infectious environmental exposures, or have an auto-immune aetiology on a background of genetic susceptibility (5).

There is no known cure for sarcoidosis and oral glucocorticoids are the standard first-line treatment (2-4). However, a review of the literature suggests that data on efficacy are lacking (2, 4), and that corticosteroids are palliative not curative with potentially major side effects (6). Up to 74% relapse after stopping corticosteroids (7).

Dysregulated calcium metabolism is another recognised complication of sarcoidosis (8, 9), resulting in prevalence of 5-10% for hypercalcaemia, 40-62% for hypercalciuria and 40-55% for reduced bone density aggravated by corticosteroids (8-10).

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THE EVIDENCE FOR MYCOBACTERIA IN SARCOIDOSIS

Infectious agents have been suspected in causing sarcoidosis since the early 1900's with Mycobacteria considered the likely culprit (11-14). Cell wall-deficient bacteria which later reverted to acid-fast bacilli have been isolated from sarcoid tissue (12). Positive immune responses have been identified against mycobacterial (15, 16) and *Propionibacterium acnes* (16) antigens in sarcoidosis bronchoalveolar lavage (BAL), using flow cytometry and matrix assisted laser desorption ionization imaging mass spectrometry (MALDI-IMS). Further support for the presence of a transmissible agent in sarcoidosis is the fact that some patients develop sarcoidosis after receiving a transplant from a patient with sarcoidosis (17).

The clinical, radiological and pathological similarities between sarcoidosis and tuberculosis are well known and *M tuberculosis* and *M bovis* are known to cause tuberculosis (18, 19). MAP causes Johne's disease in cattle (20), and possibly Crohn's disease (21, 22), whereas *M leprae* causes leprosy (23). A number of autoimmune diseases, including psoriasis (24) and rheumatoid arthritis (25) are also suspected to involve mycobacterial aetiology.

CASE STUDY - CARDIAC SARCOIDOSIS

In June of 2004 a routine x-ray of the subject, a previously healthy 55 y old Caucasian male with thalassaemia trait, revealed what was initially thought to be an aortic aneurysm. Further CT investigation concluded that there was mediastinal and bilateral hilar lymphadenopathy without the characteristic of pulmonary sarcoidosis. A preliminary diagnosis of lung sarcoidosis was made. Lung function tests were normal and a biopsy was considered but not carried out. The clinical advice received at the time was that the sarcoid was most likely a self-limiting disease that could spontaneously remit and may never cause significant clinical problems.

In August 2004, a cardiac echo was ordered because of mild hypertension and evidence of cardiac arrhythmia. The results reported an ejection fraction of 75% and normal size and function of the left ventricle. A follow-up echocardiographic study in Dec 2007 again was normal with LV Fractional shortening of 49.2%. In January 2011, because of indications

of episodic palpitations, RBBB and LAHB on ECG, a treadmill stress test and echocardiogram was carried out to a maximum workload of 10.2 Mets and concluded that the left ventricle was mildly dilated and showed mild concentric LV hypertrophy. A follow-up Chest CT scan in October 2011 concluded that there was no significant change since the CT scans carried out in 2004.

However, on the 15th June 2012 whilst at work, the subject experienced significant bradycardia and cardiac arrhythmia. The problem persisted and become acute overnight and the subject presented to the Emergency Department of St. Vincent's Hospital in Sydney the following day, on the 16th June 2012. A 12 lead ECG showed an almost complete third degree AV heart block, and a provisional diagnosis of cardiac sarcoidosis was made. A 2D, M-Mode Doppler echo study was carried out, which revealed mild dilation of both the LV and LA chambers, a reduction in LV fractional shortening to 32% and a reduced ejection fraction of approximately 55%.

Sarcoidosis induced hypercalciuria

On the 8th Aug 2012, some 2 months after the acute episode of CS, the subject required an emergency Suprapubic Cystostomy for urinary retention followed by multiple green laser treatments to remove large calcium oxalate deposits rarely seen in clinical practice from his prostate (Fig. 1).

Calcium supplements given to rats with foods high in oxalic acid can cause calcium oxalate to precipitate in the gut and reduce the levels of oxalate absorbed by the body by up to 97% in some cases (63, 64). Hence the subject decided to reduce his dietary intake of foods rich in oxalate, and began supplementation with Calcium Carbonate (1250 mg), Calcium Citrate (1190 mg) and Magnesium Phosphate (65 mg).

The objective was to minimise the risk of stone formation by reducing the absorption of oxalate and maximise formation of calcium oxalate in the gut and its subsequent elimination (26). It is of note that calcium oxalate is present in human sarcoid granulomas and sequesters significant amounts of iron and ferritin. In alveolar macrophage cultures, oxalate accumulates iron and stimulates ferritin production and giant cell formation (67).

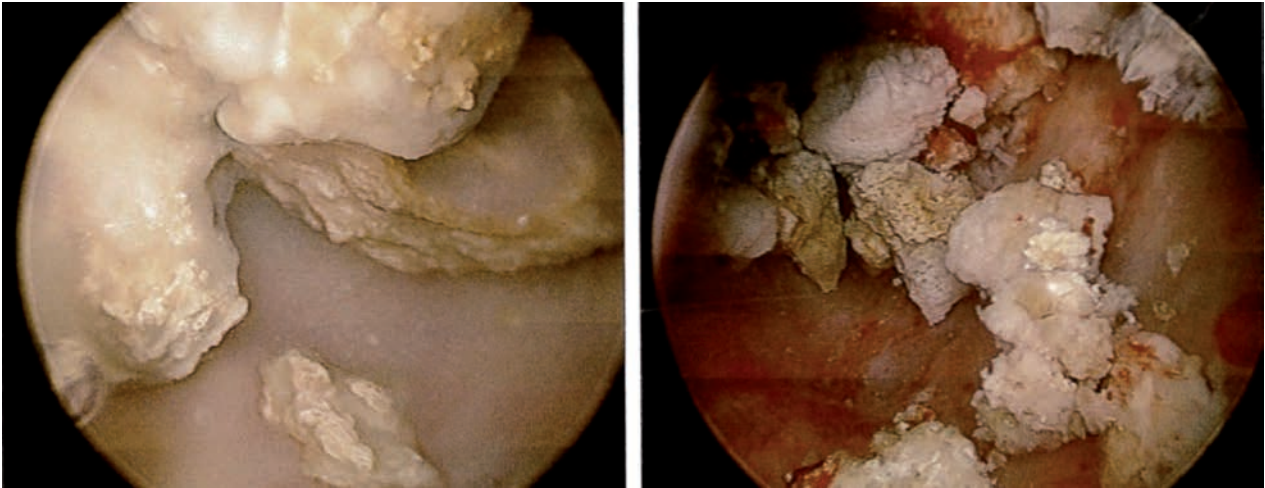


Fig. 1. Images of prostatic calcification taken during greenlight laser treatment

To alleviate the symptoms of osteoarthritis in his knees approximately 3-4 months prior to the acute episode, the subject began supplementation with Krill oil (or approximately 5000 IU of Vitamin D).

Left ventricular function and cardiac PET

On the 20th June 2012, shortly after admission to hospital with suspected CS an NM Cardiac Sestamibi scan with CT was carried out based on myocardial perfusion with technetium and with fluoro-2-deoxy-D-glucose (F1-8FDG) and cardiac computed tomography and PET. These scans confirmed the pro-

visional diagnosis of active CS. Given the complete heart block, an ICD pacemaker was fitted on the 26th June 2012, but because of technical difficulties only a RV pacing lead was inserted.

The NM Cardiac Sestamibi scan with CT carried out on the 20th June 2012 confirmed persistent reduced perfusion to the distal inferoseptal wall apically. Reduced perfusion was also noted to the proximal septal wall. The FDG PET tomographic images showed focally increased glucose metabolism in the proximal septum of the left ventricle, with a further focus of increased metabolism in the distal lateral wall. The proximal septal abnormality corresponded to a region of reduced perfusion, while the region of

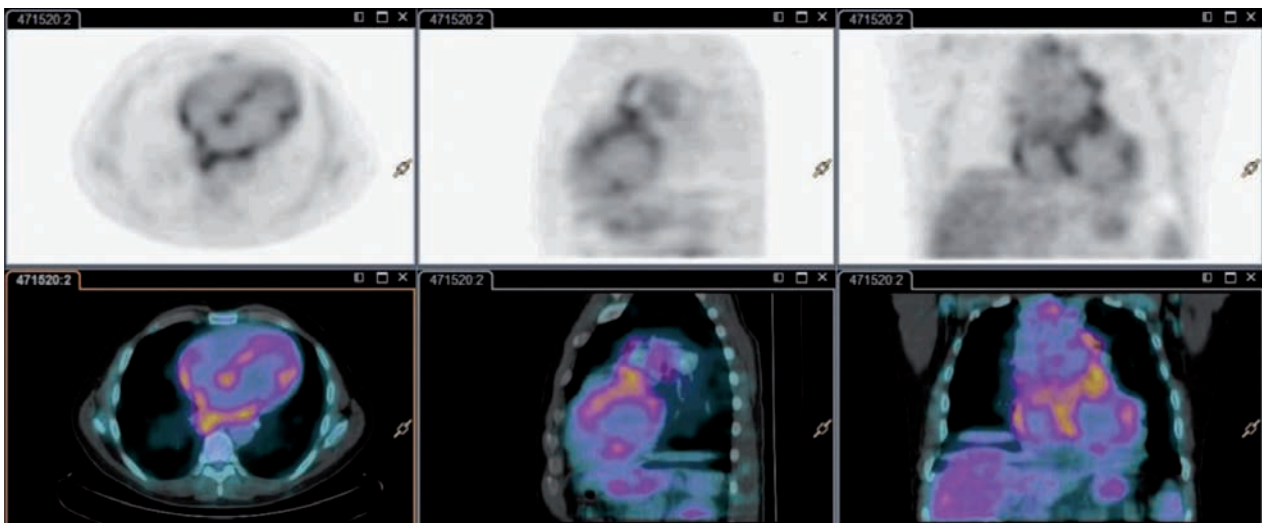


Fig. 2. Images of June 2012 PET scan showing active cardiac sarcoidosis

increased metabolism in the distal lateral wall demonstrated normal myocardial perfusion. The gated SPECT images showed a mild global hypo-kinesis with a LVEF calculated at 40%

Subsequent PET/CT Cardiac Studies results

On the 8th Oct 2015, a little more than 3 years since the acute episode of cardiac sarcoidosis and the implanting of the ICD, a follow up PET/CT cardiac sarcoid study was performed using similar methods to those described in the earlier PET/CT scan on the 20th Jun 2012. Myocardial perfusion was not dissimilar to the previous scan, with a small area of reduced perfusion in the distal inferoseptal wall, and uniform perfusion throughout the rest of the LV myocardium. Gated SPECT gave a LVEF of 38%, similar to the 37% previously recorded.

FDG PET-CT imaging showed a small area of mild increased FDG uptake in the distal inferoseptal wall, lesser both in extent and in metabolic activity in comparison to the previous 2012 study. However a prominent increased FDG uptake involving the lateral wall, much larger in extent in comparison with the previous study in 2012, was noted. In addition, hypermetabolic non-enlarged lymph nodes were observed in the left neck and right supraclavicular fossa. These areas were not imaged in 2012.

By 2016, the subject had been RV paced 3 years for 96% of the time with his LVEF deteriorating from approximately 50% to 37%. He then underwent cardiac resynchronization therapy (CRT) on the 16th Nov 2016 with right ventricular sense triggered left ventricular pacing with a LV pacing lead implanted. This led to an immediate shortening of the QRS duration from 220msec to approximately 160msec but no immediate change in LVEF.

Culturing mycobacteria and MAP antibiotic therapy

There are considerable data to strongly implicate the role of mycobacteria in sarcoidosis (11-16). Live bacteria have been found, with significant frequency, in sarcoid tissue. They are called Cell Wall Deficient (CWD), or L-Forms, or coccoid forms. These bacteria are very small, and difficult to see without special stains. They are difficult to culture and are rarely identified during conventional laboratory testing. It may be that several subspecies of bacteria may cause

sarcoidosis and not all of them are necessarily present in any one patient. Hence there are no routine laboratory tests that can identify MAP in blood and no reliable culture methods to demonstrate viability.

However in 2004, Naser et al (28) used novel culture media to successfully culture mycobacterium avium subspecies paratuberculosis (MAP) from the blood of patients with Crohn's disease. These results were subsequently replicated by Geary et al (29) who used Ziehl-Neelsen staining to show spheroplastic phase forms of MAP within the cytoplasm of a macrophage and persisting in modified TB broth after 4 months of culture.

An encounter between the subject and Prof. Tom Borody from the Centre for Digestive Diseases in Sydney led to a discussion on the similarities between mycobacteria thought to cause Crohn's disease and those implicated in sarcoidosis. Borody routinely sends blood samples from his Crohn's patients to be cultured for MAP at a laboratory in New Zealand (Otakaro Pathways) which uses novel techniques to culture MAP in blood from patients with Crohn's and livestock with Johne's disease.

Following routine blood tests, as well those for Yersinia Antibodies (Neg), Cytomegalovirus IgG (Detected), Cytomegalovirus IgM (Neg), Quantiferon-TB Gold Assay (Neg) and Strongyloides IgG (Neg) in Dec 2015 the subject had his blood sent to Dr. John Aitken who cultured the subject's white blood cells for MAP.

RESULTS

The culture, reported on 1st February 2016 showed the presence of Mycobacteria which exhibited significant growth over the 30d incubation period (Figure 3).

Some cell rupturing was present as shown in figure 3, along with "persister" forms thought to represent preliminary growth and production of biofilm, and daughter forms showing evidence of active proliferation. Photomicrographs (Figure 3) showed intracellular large forms, with a group of small forms also visible in the upper right quadrant. The blue masses are macrophages, some in the process of disintegrating. The report concluded that the overall appearance is similar to that seen in other "autoimmune diseases", such as Crohn's disease.

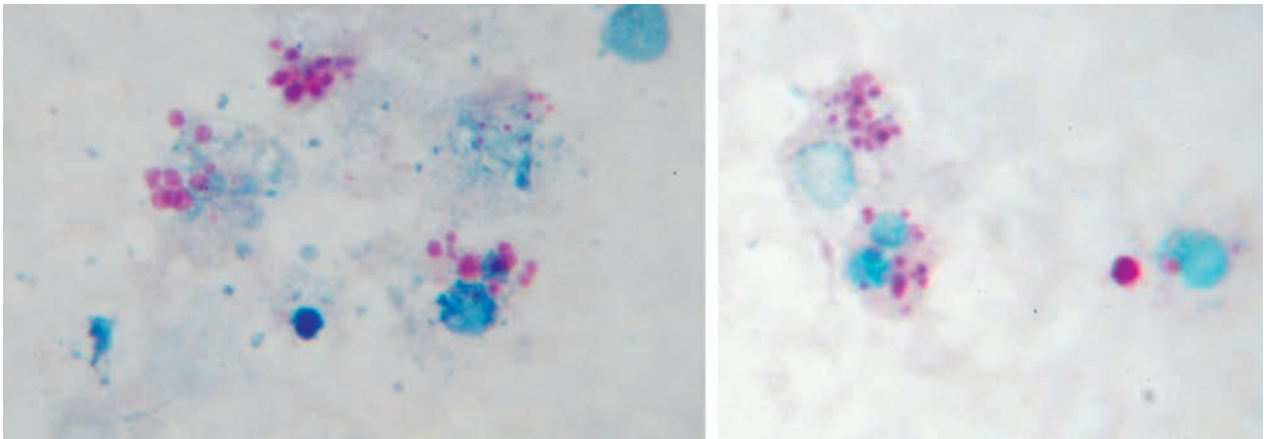
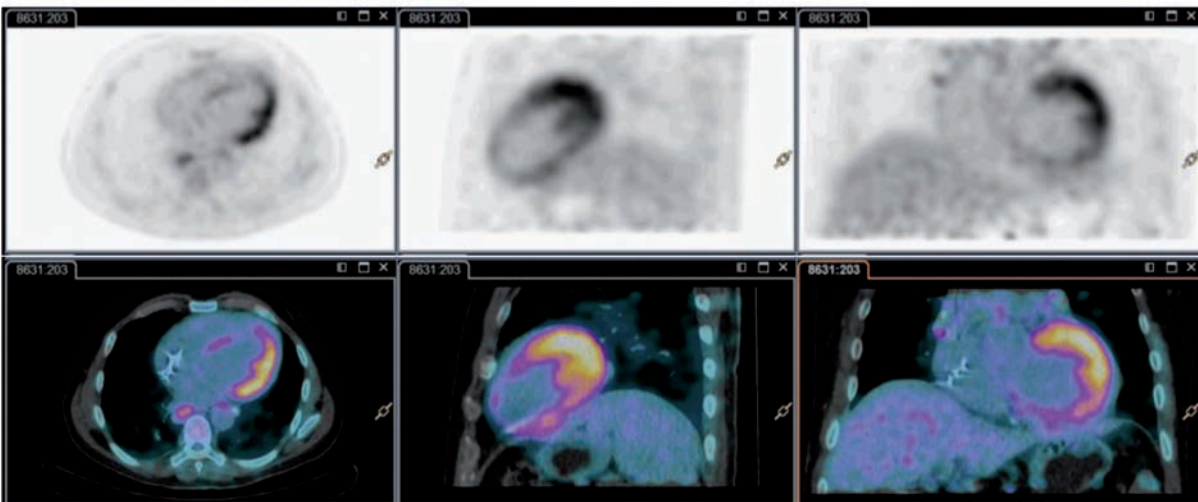


Fig. 3. Photomicrographs of 30 day culture samples

Panel A. PET/CT scan, October 2015



Panel B. PET/CT scan, March 2017

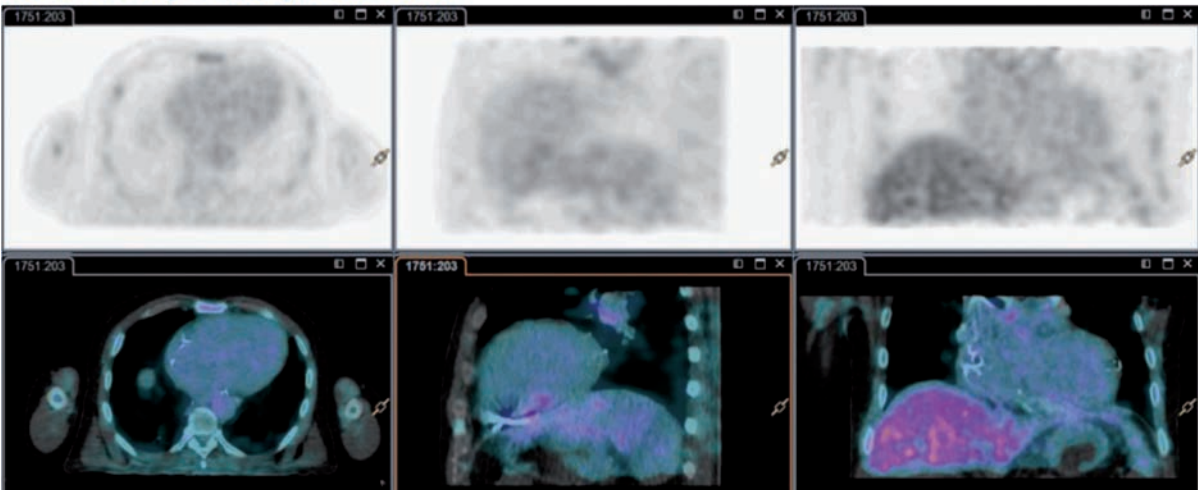


Fig. 4. Comparison of October 2015 PET/CT scan with March 2017 scan of avid regions of the myocardium

Hence, with the agreement of the subject, Borody commenced ramping-up anti-MAP therapy on 4th Feb 2016 with Rifabutin (150 mg), Clarithromycin (250 mg) and Clofazimine (150 mg) mane and Metronidazole (200 mg) BD. This was increased at six weeks to maintenance doses of Rifabutin 150 mg, Clarithromycin 250 mg, Metronidazole 400 mg BD and Clofazimine 150 mg mane monitored by periodic blood tests.

On the 3rd Mar 2017, a little more than one year since the start of MAP therapy, a radionuclide time-of-flight FDG PET-CT cardiac sarcoid study was carried out. Although similar to the study carried out in 2015, the body was imaged from the vertex of the skull to the mid-thigh.

The PET Cardiac scan in March 2017 (30) revealed complete resolution of all FDG PET avid regions in the myocardium, compared to the two previous studies in 2012 and 2015. The sestamibi (MIBI) myocardial perfusion images continued to demonstrate persistently reduced perfusion to the inferoseptal wall apically. The LVEF remained impaired at 38%. No FDG avid pulmonary nodules or pleural effusions as well as mediastinal or distant lymphadenopathy were observed. Liver, spleen, kidneys, pancreas and bowel were all normal.

CONCLUSIONS

The March 2017 PET Cardiac scan revealed complete resolution of all FDG PET avid regions in the myocardium, compared to the two previous studies in 2012 and 2015 assumed to be the consequence of Anti-MAP therapy aimed at sarcoid MAP.

The effect of antibiotic MAP therapy in promoting *complete resolution* of all FDG PET avid regions in the myocardium, with no FDG avid pulmonary nodules or pleural effusions as well as mediastinal or distant lymphadenopathy observed, compared to the two previous studies in 2012 and 2015 is encouraging and suggests that viable mycobacteria are being killed by the antibiotic MAP therapy, although dormant forms may still be present.

These results of antibiotic MAP therapy, as evidenced by complete resolution of all FDG PET avid regions in the myocardium, has never been previously reported.

RECOMMENDATIONS

Cardiac sarcoidosis may be the result of intracellular Mycobacteria that can be cultured, are viable, and that, based on PET/CT scan results presented, anti-MAP therapy can completely resolve the active disease.

Now that mycobacteria are beginning to be cultured and isolated and PCR analysed, and DNA sequencing carried out, patients should endeavour to avail themselves of blood MAP culture to open the door to Anti-MAP therapy.

A diagnosis of sarcoidosis, should never be ignored even though the condition may appear to be in complete remission.

Sarcoidosis presents a special case of Vitamin D and calcium dysregulation and blind supplementation should not be offered to sarcoidosis patients nor be accepted, as it may exacerbate symptoms or activate the dormant sarcoidosis.

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