

Case Study

Transplant surgery as a treatment for organ failure due to sarcoidosis

Sula Cotterell¹ and James Gilbert²

¹Medical Sciences Division, University of Oxford, UK

²Consultant Transplant & Vascular Access Surgeon, Oxford Transplant Centre, OUH

Keywords:

Sarcoidosis, renal transplant, transplant surgery.

Key Learning Points

James Gilbert

Sarcoidosis is a rare inflammatory disease of unknown aetiology that can affect different organs and tissues of the body. The disease process is characterised by the formation of non-caseating granulomas which often affect multiple sites and can lead to progressive organ failure. Sarcoidosis is seen most commonly in the lungs but when the granulomas form in the kidney, the condition is called renal sarcoidosis.

Renal Sarcoidosis is thought to occur in about 35-50% of sarcoidosis patients and if discovered late or left untreated, it can lead to renal failure. Although interstitial granulomatous nephritis is the most typical histological finding on a renal biopsy, it is actually disordered calcium metabolism that leads to progressive chronic kidney disease and, in rare cases end stage renal failure requiring dialysis or transplantation.

Although transplant surgery has been used as a treatment for patients with Sarcoidosis, it has mainly been in the form of lung and liver transplant. The 1 and 5-year outcomes in these patients when compared with non-sarcoidosis lung and liver transplant recipients are very similar suggesting that Sarcoidosis is not a contraindication to transplant surgery.

There are very few reported cases of renal transplantation as a form of treatment for patients with end-stage kidney disease secondary to renal sarcoidosis. Cases series previously published have highlighted acceptable long-term patient and allograft survival rates. There are incidences of Sarcoid recurrence and de-novo sarcoidosis in transplanted kidneys, but these numbers are small, and it is not clear whether there should be specialist monitoring out with routine transplant follow-up practices. We report a case of a renal transplant undertaken for renal sarcoidosis in our institution over a year ago.

Introduction

Patient R is a 61-year-old former pilot, who was diagnosed with renal sarcoidosis in 1990. Since then he has suffered chronic renal failure secondary to the sarcoidosis, leading to him receiving a living related donor kidney transplant, donated by his son, in April 2019.

Sarcoidosis is a multi-system disease of unknown cause, involving the formation of granulomas in affected tissues. The prevalence in the UK is around 1 in 10,000. It most commonly affects the lungs, but can affect many other organs, such as the kidneys in the case of patient R.

Here I review the use of transplant surgery to treat organ failure induced by sarcoidosis. Sarcoidosis is currently an uncommon reason for requiring transplant surgery, but there is little evidence of any difference in long term survival or graft rejection between sarcoidosis and other causes of organ failure. This indicates that although sarcoidosis may be an uncommon condition, and organ failure due to sarcoidosis even more uncommon, it can be treated by transplant surgery like many other causes of organ failure.

Case Report

History of presenting complaint

Patient R's renal sarcoidosis was detected before he experienced any symptoms, during an RAF health check in 1990. He was found to have blood test results suggestive of abnormal kidney function (including raised creatinine), and therefore underwent a biopsy on his kidneys, which showed renal sarcoidosis.

At the time of his transplant, patient R was in pre-dialysis renal failure. His eGFR has been monitored since his sarcoidosis diagnosis, and by June 2018 had fallen to 18 ml/minute, on a steady downward trajectory. On a recent ultrasound scan, his native kidneys were observed to be small, with reduced cortico-medullary differentiation. Over the year prior to his transplant, he had experienced progressive fatigue, which had begun to limit his lifestyle. He also had an episode of anaemia in late 2018 as a result of his renal failure, for which he required intravenous iron infusion.

Past medical history and drug history

Patient R has also suffered other health problems from his sarcoidosis. His lungs have been affected, resulting in scarring. This has left him with a persistent cough. Patient R has also had hypercalcaemia in the past due to his sarcoidosis. Hypercalcaemia can lead to nephrocalcinosis in sarcoidosis patients, which may have also contributed to patient R's renal failure. Aside from sarcoidosis, patient R's medical history consists only of a stroke in 2008, which has not left him with any functional deficit.

Prior to his transplant, patient R was taking sodium bicarbonate tablets, atorvastatin, felodipine and aspirin. He is a non-smoker, drinks a moderate amount of alcohol, and has no allergies. He has no family history of any health conditions, renal or otherwise.

Surgical management

Patient R underwent a living related donor kidney transplant in April 2019, with his son as the donor. The HLA mismatch was 1-1-1. The son's left kidney was removed laparoscopically in the morning and implanted into patient R's right iliac fossa in the afternoon. The donor kidney's artery and vein were anastomosed to the native external iliac artery and vein respectively. The donor kidney ureter was anastomosed directly with the bladder, with insertion of a double J stent into the ureter to help prevent post-operative blockage or leaking. During the operation, donor kidney function began as soon as the arterial clamps were removed, with visible urine production. Correspondingly, patient R's creatinine level began to fall immediately after the operation. Post-operatively, patient R was prescribed tacrolimus and mycophenolate as immunosuppression, alongside antiviral and antibiotic prophylaxis, and pain relief.

Outcome

Twelve months post-transplant, patient R is in good health. In March 2020, his eGFR was 58 ml/minute, indicating continuing allograft function (by comparison, pre-transplant eGFR in June 2018 was 18 ml/minute), and all other transplant blood tests were satisfactory.

Discussion

Treatment of sarcoidosis with surgery

Sarcoidosis is a rare condition involving the formation of non-caseating granulomas, often affecting multiple sites¹. Sarcoidosis most commonly affects adults aged 20 to 40, and has the highest prevalence in Northern Europe. It affects around 1 in 10,000 people in the UK. The cause of sarcoidosis is not known, but there are certain alleles associated with sarcoidosis such as HLA-DRB1. Granuloma formation can occur in many different tissues, and consists of accumulation of epithelioid macrophages, multinucleate giant cells and activated T lymphocytes. These most commonly affect the lungs. As such, around 90% of sarcoidosis patients have an abnormal chest X-ray, and this is often how a sarcoidosis diagnosis is reached, as it may be otherwise asymptomatic. Sarcoidosis often resolves spontaneously, and so most cases are not treated. As the disease process appears immune system driven, corticosteroids can be used in cases with severe symptoms or unfavourable prognostic features, such as symptomatic parenchymal lung disease, neurological or cardiac involvement, hypercalcaemia, or uveitis. In more severe cases, intravenous methylprednisolone, immunosuppression (such as methotrexate), or anti-TNF α

therapy can be considered.

Sarcoidosis can affect almost any body tissue, with varying frequency. However, sarcoidosis in certain organs can lead to organ failure, occasionally requiring organ replacement therapy. Transplant surgery has been used to treat sarcoidosis induced organ failure in the kidney (as seen in patient R), the heart, the lungs and the liver. In the US in 2006, around 3% of lung transplants and less than 1% of heart and liver transplants were performed in patients with sarcoidosis (however, not all of these were necessarily due to sarcoidosis induced organ failure)². When comparing survival data, the 1- and 5-year survival rates were similar between sarcoidosis and non-sarcoidosis recipients for lung and liver, and slightly higher in sarcoidosis recipients for heart transplant. This provides an initial indication that sarcoidosis should not be a contraindication to transplant surgery.

Lung transplant

The granulomatous process of sarcoidosis in the lungs most commonly leads to bilateral hilar lymphadenopathy, fibrosis, and pulmonary infiltrates¹. In turn, this leads to the symptoms of a dry cough (as seen in patient R), progressive dyspnoea and reduced exercise tolerance, and chest pain. Lung transplantation can be the only treatment option left when sarcoidosis progresses to severe pulmonary fibrosis which is unresponsive to medical interventions. Lung transplant is a major operation and is not commonly carried out, however several studies indicate that lung transplant for sarcoidosis is not associated with worse outcome than for any other cause of lung disease. In particular, one large study in 2016 looking at 20,896 lung transplant recipients, 695 of which had pulmonary sarcoidosis, found that sarcoidosis was not associated with worse mortality than non-sarcoidosis patients³. The median survival in the two groups was similar: 69.7 months in the sarcoid group, and 63.1 months in the non-sarcoid group. The rates of complications such as new O₂ requirement or bronchioalveolitis obliterans syndrome were also similar. There was no association between sarcoidosis and allograft dysfunction, and fewer sarcoidosis recipients went on to have re-transplantation (2.2% of sarcoid patients vs 3.8% of non-sarcoid). These results are reinforced by an earlier study in 2008, where specifically bronchioalveolitis obliterans syndrome was studied as a complication in sarcoidosis lung transplant recipients⁴. Again, both the survival rates and complication rates were similar between the sarcoidosis recipients, and the control group who received transplants for idiopathic pulmonary fibrosis. It has been observed in some cases of transplantation for pulmonary sarcoidosis that the sarcoidosis can recur in the allograft⁵. However, this does not affect survival or complication risk. Lung transplant surgery for pulmonary sarcoidosis is not associated with worse prognosis than when used for any other lung pathology, and therefore it should be considered as a treatment for sarcoidosis which has progressed to severe pulmonary fibrosis, just as it would be in any other case of lung failure.

Heart transplant

The frequency of sarcoidosis affecting the heart is unclear as it is thought that most cases are asymptomatic, and many are only detected post-mortem. Estimates of the percentage of cardiac disease remaining undetected (based on autopsy studies) vary, some up to 70%⁶. One autopsy study also suggested that 25% of all sarcoidosis patients have some cardiac involvement⁷. Sarcoidosis can have a

huge variety of effects on the heart, including heart block, arrhythmias, heart failure, pericardial disease and valvular dysfunction⁶. Some of these may be detected on ECG and so all sarcoidosis patients should have their ECG checked, as ventricular arrhythmias could lead to sudden death. Heart transplant has been used for cardiac sarcoidosis in a number of reported cases, as the untreated prognosis can be poor particularly when features such as ventricular arrhythmias or ventricular dysfunction appear. One particular worry in transplant for cardiac sarcoidosis is the possibility of complications due to extracardiac sarcoid, such as pulmonary hypertension from pulmonary disease, which may affect heart transplant function⁸. A study by Rosenthal et al. in 2018 compared the outcomes of heart transplants in 12 patients with cardiac sarcoid, and 28 patients with non-ischaemic cardiomyopathy⁹. They found that neither rejection rate nor mortality were significantly higher in the sarcoid compared to non-sarcoid groups. Measures of allograft function such as right ventricular stroke index were also comparable between the two groups. None of the sarcoidosis patients in this study developed recurrence of cardiac sarcoidosis. Regarding the risk of pulmonary sarcoidosis complications, despite 58% of the cardiac sarcoidosis patients also having pulmonary sarcoidosis, none of them developed pulmonary hypertension or raised pulmonary vascular resistance following surgery, indicating that pulmonary sarcoidosis alone should not prevent treatment of cardiac sarcoidosis with transplant. However, pre-existing pulmonary hypertension due to sarcoidosis may be a contraindication to heart transplant, as would be the case if the hypertension were due to other pulmonary pathologies. A slightly larger study in 2018 (including 67 cardiac sarcoidosis transplants) also looked in part at survival after heart transplant between cardiac sarcoidosis and non-sarcoidosis patients, and similarly found that the survival between the two groups was not significantly different¹⁰. As these studies indicate that cardiac sarcoidosis does not have any impact on the survival or graft function post-transplant, heart transplantation should continue to be considered in cases of cardiac sarcoidosis with poor prognostic features such as ventricular arrhythmias.

Kidney transplant

There are two main ways in which the kidney can be affected by sarcoidosis: either by effects on calcium metabolism or directly by granulomatous changes⁶. Activated macrophages in sarcoidosis produce calcitriol, which can lead to hypercalcaemia, hypercalciuria, nephrocalcinosis, or kidney stones. Nephrocalcinosis alone can produce chronic renal failure. Granulomatous changes in the kidney can also lead to tubulointerstitial nephritis. Inflammation of the tubules prevents them from concentrating urine, leading to polyuria, GFR reduction and elevated creatinine, alongside systemic symptoms such as fatigue. It is likely that as patient R had both renal sarcoidosis and episodes of hypercalcaemia, both nephrocalcinosis and tubulointerstitial nephritis played a part in his kidney failure. Sarcoidosis rarely causes end stage renal failure, however, making the case of patient R unusual. As such, renal transplant has not been reported in many sarcoidosis patients. One study in 2010 followed 18 sarcoidosis patients after renal transplant, although only 10 of these patients had renal failure due to renal sarcoidosis¹¹. After a mean follow-up of 4 years, the patient survival and death-censored graft survival were 94%. The mean GFR at 4 years was 60 ml/min, which is reasonable function for a transplant kidney. However, 5 patients had

a sarcoidosis recurrence during the follow up period, 3 of which occurred in the transplanted kidney. A case study in 2013 reported another patient who developed sarcoidosis in a transplant kidney, despite there being no previous sarcoidosis diagnosis¹². The allograft was found to have non-necrotising granulomatous interstitial nephritis upon biopsy, 3 years after the transplant. There have been few studies into renal transplant in sarcoidosis, although current evidence suggests that end stage renal failure due to sarcoidosis can be treated just as effectively with transplant surgery as other more common causes of renal failure. However, reports of sarcoidosis recurrence in renal transplants¹³ suggest that clinical and histological monitoring would be needed to detect and treat any recurrence of renal sarcoidosis.

Liver, pancreas, and intestinal transplant

Sarcoidosis can affect nearly any body tissue. The liver is frequently affected, although this is rarely symptomatic⁶. Most commonly, hepatic sarcoidosis causes hepatomegaly, with granulomas being found in 50-65% of patients. However, in rare cases sarcoidosis can lead to cirrhosis, and some patients may develop advanced liver disease. Liver transplant has been used to treat hepatic sarcoidosis, and one study from 1993 compares outcomes between transplants for hepatic sarcoidosis, cholestatic liver disease, and parenchymal non-sarcoidosis liver disease¹⁴. It was found that there was no statistical difference in either allograft or patient survival between the sarcoidosis and non-sarcoidosis groups. This study also proposed that the immunosuppression used after the transplant procedure may have helped to cause remission of sarcoidosis, as there was no evidence of disease progression or continued activity in extra-hepatic sites such as the lungs in the sarcoidosis patient group.

Sarcoidosis in the gastrointestinal tract is uncommon, occurring in under 1% of sarcoidosis patients. Gastrointestinal sarcoidosis most commonly affects the stomach, although it has also been reported in the oesophagus, colon, rectum, appendix and pancreas⁶. Alongside lung, heart, kidney and liver, transplant of small bowel and pancreas are the main other solid organ transplants currently carried out. It is uncommon for either the small bowel or the pancreas to be severely affected by sarcoidosis, and therefore the likelihood of needing organ replacement treatment is low. However, evidence from transplant of other organs affected by sarcoidosis indicates that transplants of pancreas and small bowel should also be suitable following sarcoidosis, should this clinical scenario arise.

Conclusions

The case of patient R indicates that organ transplantation is a suitable treatment for organ failure due to sarcoidosis, just as in many other causes of organ failure. In this review of transplantation for sarcoidosis across multiple different organs, there is no evidence of increased allograft rejection or decreased patient survival when compared to any of the non-sarcoidosis control groups. In some organ transplants there are reports of recurrence of sarcoidosis within the allograft, particularly in kidney transplantation. In light of this, there is a chance of sarcoidosis recurrence in patient R, however this does not mean that his survival chances are decreased. There has been some suggestion that although the cause of sarcoidosis is unknown, it is an immune driven granulomatous process, and therefore the post-transplant immunosuppression may

in fact act to suppress sarcoidosis⁹. It may also be that only the immediate post-operative heavy immunosuppression acts to suppress sarcoidosis, and once the dose is reduced to a maintenance level the risk of sarcoidosis recurrence returns, which could explain episodes of post-transplant sarcoidosis¹⁵. However, further work into the effect of post-transplant immunosuppression regimes on sarcoidosis, and on the disease process of sarcoidosis itself are both needed to fully understand the reports of sarcoidosis recurrence following transplant surgery. Although the interaction between post-transplant immunosuppression and sarcoidosis recurrence is still unclear, current evidence suggests that in sarcoidosis induced organ failure, transplant surgery is a viable and effective treatment option.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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