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CASE REPORT

INTERMEDIATE

CLINICAL CASE

ATGL Deficiency-Induced Triglyceride Deposit Cardiomyovasculopathy Requiring Heart Transplant

A 5-Year Follow-Up

Prina Rajani, MBBS,[a] Jan Lukas Robertus, PhD,[a] Joyce Wong, PhD,[a] Tessa Homfray, MBBS,[a] Fernando Riesgo Gil, MD,[a] Mayooran Shanmuganathan, MBBS[a,b]

ABSTRACT

A young man presented with syncope. He was diagnosed with triglyceride deposit cardiomyovasculopathy and skeletal myopathy secondary to adipose triglyceride lipase (ATGL) deficiency. Despite optimal medical therapy, he required heart transplantation to treat his heart failure. Five years post-transplant, the graft function was normal with no evidence of triglyceride deposits. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:760–3)

HISTORY OF PRESENTATION

A 22-year-old male presented with syncope for the first time. Since childhood, because of mild dyspnea and myalgia, he had reduced exertional capacity when compared with his peers but this had not been medically evaluated.

MEDICAL HISTORY

He had no formal medical history nor any family history. His parents were first cousins of South Asian origin.

LEARNING OBJECTIVES

- To be aware that lipid storage diseases, such as ATGL deficiency, can cause heart failure.
- To appreciate that heart transplantation is an effective cure for triglyceride cardiomyovasculopathy.

EXAMINATION

There was a pansystolic murmur in the mitral region with no signs of fluid overload. Cranial nerve examination was normal. There was wasting of the upper limb muscles with proximally distributed weakness. The lower limb weakness was distally distributed. All reflexes were absent but with normal plantar reflexes. Sensation was normal.

DIFFERENTIAL DIAGNOSIS

Multisystem involvement and parental consanguinity raised the suspicion of a recessively inherited myopathic disorder.

INVESTIGATIONS

Electrocardiogram showed poor R wave progression and Troponin I was mildly elevated. Echocardiogram

From the [a]Heart Transplant Department, Royal Brompton and Harefield NHS Foundation Trust, Oxford, United Kingdom; and the [b]Cardiovascular Medicine, University of Oxford, Oxford, United Kingdom. The authors have reported that they have no relationships relevant to the contents of this paper.

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and cardiac magnetic resonance (CMR) imaging demonstrated a severely dilated and impaired left ventricle with thinning and akinesis of the inferolateral wall, extending from the base to the apex. The left ventricular ejection fraction was 20% to 25%. All other walls were thin and hypokinetic. Late gadolinium imaging showed subendocardial enhancement in the anterolateral and inferior walls in an unusual pattern, not typical for coronary disease (Figures 1A and 1B). The coronary angiogram was normal.

Creatine kinase (CK) was 1,600 u/l (normal range 22 to 198 U/l). Electromyography confirmed prominent myopathy affecting both distal and proximal muscle fibers. Skeletal muscle and skin biopsies showed myocytes vacuolation raising the suspicion of a lipid myopathy. Exome sequencing revealed homozygosity for the c.497A>G (p.Asp166Gly) mutation in the PNPLA2 gene. This causes excessive lipid storage in myocytes (1).

MANAGEMENT

He was treated with optimal guideline directed medical therapy and cardiac resynchronization therapy-defibrillator. He remained stable for 18 months. In the following 12 months, he was hospitalized 4 times with decompensated heart failure. His symptoms deteriorated from New York Heart Association functional class I to IV.

He was hospitalized again due to repeated but appropriate cardiac resynchronization therapy-defibrillator shocks. Echocardiogram showed a decrease in left ventricular ejection fraction (10% to 15%). Thus, he was referred for an assessment to receive mechanical circulatory support ± heart transplant.

On arrival to the transplant center, he exhibited signs of inadequate cardiac output with renal and hepatic dysfunction requiring inotropic support. Right heart catheter study showed severely reduced cardiac index (1.3). Left ventricular endomyocardial biopsy (EMB) showed myocyte enlargement with cytoplasmic vacuolation in a lace-like pattern (Figure 2A). This confirmed the diagnosis of triglyceride deposit cardiomyovasculopathy (2) and helped to exclude other causes of heart failure.

His case was discussed at the transplant multidisciplinary meeting. Besides his mild neuromuscular weakness, he had no other comorbidities and thus he was placed on the urgent waiting list for a heart transplant. However, despite being on inotropic support, his condition deteriorated rapidly and he developed cardiogenic shock. Therefore, a biventricular assist device was implanted to maintain end-organ perfusion and bridge him to heart transplantation.

ABBREVIATIONS AND ACRONYMS

ATGL = adipose triglyceride lipase

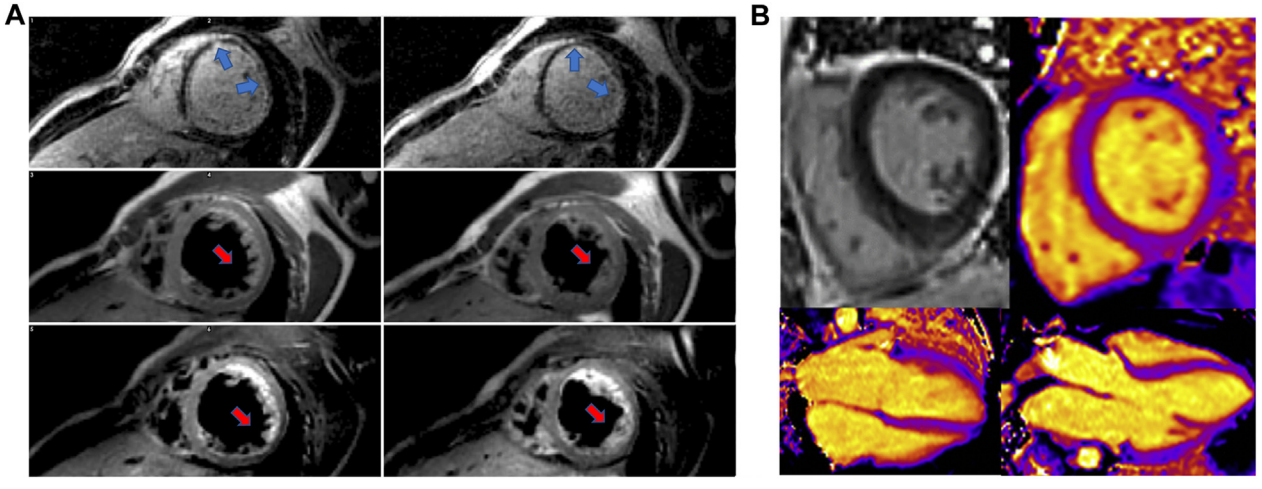
CK = creatine kinase

CMR = cardiac magnetic resonance

EMB = endomyocardial biopsy

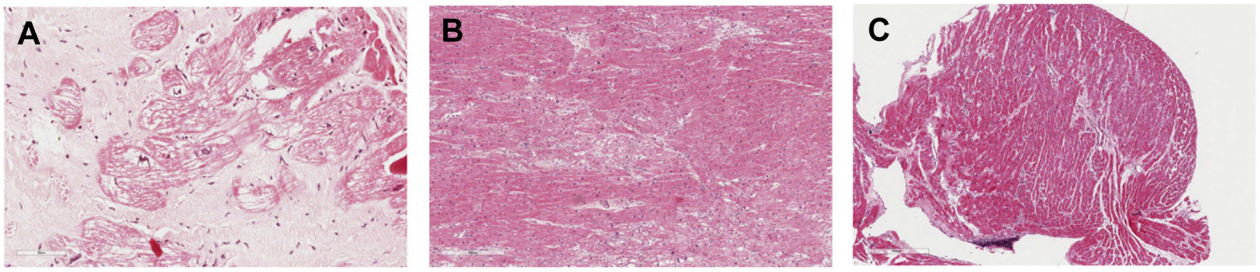
PNPLA2 = patatin-like phospholipase domain containing 2

FIGURE 1 CMR Before and After Transplant



(A) Diseased native heart: CMR late gadolinium enhancement imaging (LGE) in the short-axis plane demonstrating subendocardial and mid-wall delayed enhancement, predominantly in the anterior and lateral walls **(blue arrows)**. Fat saturated imaging showed a reduction in signal in the inferolateral wall suggestive of fat infiltration **(red arrows)**. **(B)** Transplanted heart at 5 years: CMR parametric T1 mapping did not show fat infiltration of the transplanted heart. LGE was also unremarkable.

FIGURE 2 Cardiac Biopsies Before and After Transplant



(A) Diseased native heart: EMB of the left ventricle showing myocyte enlargement with cytoplasmic vacuolation in a lace-like pattern, and patchy degeneration, and drop-out with fibrous replacement. Some nuclei are enlarged, stretched, and indented by vacuoles. No active inflammation. No excess glycogen nor mucin on periodic acid-Schiff (PAS) and diastase-PAS stains (hematoxylin and eosin [H&E] stain, 200×). **(B)** Diseased native heart: sections taken from the left ventricle of the explanted heart shows similar morphological appearances as in **A**. There is interstitial fibrosis associated with small lymphocytes and hypertrophied myocytes with variable cytoplasmic vacuolation (H&E 40×). **(C)** Transplanted heart: EMB of the right ventricle shows a quilty lesion, interstitial fibrosis, and mild increase of cellularity. There is no vacuolization in the cardiomyocytes (H&E 40×).

After 4 weeks, he received a heart transplant. Postoperatively, he was put on extracorporeal membranous oxygenation support for 3 days because of severe primary graft dysfunction. EMB excluded acute allograft rejection.

He had a prolonged stay in the intensive care unit of 125 days, mainly because of slow respiratory weaning. His preexisting neuromuscular weakness and being critically ill before the transplant surgery were likely to be the contributing factors.

FOLLOW-UP

Five years post-transplant, he continues to be followed up by neurologists. Although there is no cure for the neuromuscular condition, he does not report any deterioration.

In the transplant clinic, he denied any cardiac symptoms. His CK was raised at 2,628 U/l (normal range 22 to 198 U/l) and troponin I was 46 ng/l (normal <19 ng/l). This prompted a repeat CMR and EMB. CMR showed normal left ventricular function (left ventricular ejection fraction 62%) and no evidence of fat infiltration or fibrosis in the transplanted heart (**Figures 1B** and **2C**). The EMB of the right ventricle did not show any triglyceride deposits nor signs of rejection.

DISCUSSION

Adipose triglyceride lipase (ATGL), coded by the patatin-like phospholipase domain containing 2 (PNPLA2) gene, is the enzyme responsible for the first step of triglyceride hydrolysis (3,4). Mutations in the PNPLA2 gene lead to reduced messenger RNA levels of peroxisome proliferator-activated receptors target genes (5,6). This results in the autosomal recessive disorder, neutral lipid storage disease with myopathy, where there is excessive cytoplasmic lipid accumulation in organs and tissues throughout the body (5,6).

Approximately 90 patients with neutral lipid storage disease with myopathy from a variety of ethnic groups have been clinically and genetically characterized (1–9). Patients usually present with proximal muscle weakness in their late 20s and early 30s (6,8). Some go on to have distal limb involvement (9). Serum CK levels remain elevated throughout (6,8,9). Approximately 40% of patients exhibit cardiac dysfunction which appears to be affected later in the course of the disease, usually after the age of 20 (2,3,5–9).

The extent of cardiac involvement is influenced by many factors as evidenced by siblings who carry the same ATGL mutation (3,5–9). Estrogen appears to have a protective effect demonstrated by the higher incidence of cardiac damage in male patients (3,8). Similarly, there is ethnic disparity of cardiac involvement as none of the 45 Chinese patients described by Zhang et al. (9) had a severe cardiac phenotype (9).

Only 2 cases of triglyceride deposit cardiomyovasculopathy secondary to ATGL deficiency required left ventricular assist device and later, heart transplant (2). Our case adds a third example of this and for the first time describes a 5-year follow-up after heart transplant with CMR images and EMB histology, demonstrating that the donor heart is free of triglyceride deposits.

CONCLUSIONS

We describe a very rare case of a patient with triglyceride deposit cardiomyovasculopathy secondary to ATGL deficiency. This led to advanced heart failure requiring heart transplantation. For the first time, we have demonstrated with supporting CMR and cardiac histology data that heart transplantation offers a cure for triglyceride deposit cardiomyovasculopathy, as the disease has not affected the donor heart 5 years after transplant.

ADDRESS FOR CORRESPONDENCE: Dr. Mayooran Shanmuganathan, Heart Transplant Department, Harefield Hospital, Hill End Road, Harefield UB9 6JH, United Kingdom. E-mail: m.shanmuganathan@rbht.nhs.uk. Twitter: @mayooranshan.

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