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CASE REPORTS

Heart transplantation in a patient with Myotonic Dystrophy type 1 and end-stage dilated cardiomyopathy: a short term follow-up

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Myotonic dystrophy type 1 (DM1) or Steinert's disease is the most common muscular dystrophy in adult life with an estimated prevalence of 1:8000. Cardiac involvement, including arrhythmias and conduction disorders, contributes significantly to the morbidity and mortality of the disease. Mild ventricular dysfunction has also been reported associated with conduction disorders, but severe ventricular systolic dysfunction is not a frequent feature and usually occurs late in the course of the disease. Heart transplantation is currently considered the ultimate gold standard surgical approach in the treatment of refractory heart failure in general population. To date, considering the shortage of donors that limit the achievement of a greater number of heart transplants and the reluctance of the cardiac surgeons to transplant patients with dystrophic cardiomyopathy, little is known about the number of patients with DM1 transplanted and their outcome. We report the case of a 44 year old patient with Steinert disease who showed an early onset ventricular dysfunction refractory to optimal medical and cardiac resincronization therapy, and underwent to successful heart transplantation. At our knowledge, this is the second heart transplantation performed in a patient affected by Steinert disease after the one reported by Conraads et al in 2002.

Key words: myotonic dystrophy type 1, heart transplantation, dilated cardiomyopathy

Introduction

Steinert's disease or Myotonic Dystrophy type 1 (DM1) is an autosomal dominant multisystemic disorder characterized by myotonia, muscle and facial weakness, cataracts, cognitive, endocrine and gastrointestinal involvement. Cardiac involvement affects the conduction system in about 80% of cases and usually follows the onset of myopathy (1). One third of patients with DM1 may have sudden cardiac death, likely due to the onset of malignant ventricular arrhythmias, so the early identification and treatment of the cardiac impairment is the main key to prevent this tragic event. Advanced degrees of conduction abnormalities and arrhythmias are indicated as significant predictors of mortality in patients with DM1 (2, 3). Myocardial contractility is less commonly impaired and heart failure (HF) may occur late in the course of the disease as the final stage of the cardiomyopathy (4, 5). Despite cardiac involvement, DM1 patients are usually asymptomatic, probably due to the limited level of activity and consequently reduced cardiac demand (3). Heart transplantation (HT) is currently considered the ultimate gold-standard surgical approach in the treatment of refractory heart failure (RHF), a situation in which the patients present with great functional limitation and high mortality rate (6). Thus, HT should be taken into account for patients in III and IV NYHA class, who need recurrent hospitalizations, and present with a poor prognosis despite the therapeutic optimization.

To date, because of the shortage of donors and the high operative risk related to muscle impairment and respiratory failure in patients with DM1, heart transplanta-

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tion is not considered an appropriate option in these patients (7).

We report the second case of a successful heart transplantation in patient with Myotonic Dystrophy type 1 who showed an early ventricular dysfunction, despite the employ of optimal medical and cardiac resynchronization therapy.

Case report

A 44-year-old man, affected by Steinert disease and regularly followed at the Cardiomyology and Medical Genetics of the University Hospital "Luigi Vanvitelli" since the time of his diagnosis (2003), recently needed frequent hospitalisations for exacerbations of signs and symptoms of congestive heart failure, occurred in 2016.

The diagnosis of DM1, based on family history (father and one brother affected) and presence of typical clinical features (myotonic phenomenon, mild distal skeletal muscle atrophy, cataract, gastrointestinal disturbances, endocrine deficiency), was subsequently confirmed by molecular testing, that showed a pathological expansion (500 CTG triplets). In 2005, a bicameral pacemaker (PM) was implanted because evidence of first degree (PR interval ≥ 255 ms) plus second-degree type 2 atrio-ventricular block (8-12), and concomitant episodes of paroxysmal atrial fibrillation (AF), a frequent finding in this population (13-22, 23-28). The implant was followed by an improvement of symptoms and quality of life. In 2013, the PM was uploaded to a cardioverter defibrillator (ICD), because of the detection of not sustained ventricular tachycardia (NSVT) in pacemaker stored electrograms. According to our protocol the uploading is usually performed to prevent the risk of sudden cardiac death, frequently observed in these patients as in others muscular dystrophies (29-32). At six-months follow-up, the epicardial CRT did not induce symptom relief, nor improvement of the ejection fraction (Fig. 1) or reduction of the arrhythmic risk.

Three years later during a routine cardiological check, signs of congestive heart failure (CHF) were detected. Transthoracic echocardiography showed a dilated cardiomyopathy, with a left ventricular end-diastolic diameter (LVEDD) of 7.4 cm and an ejection fraction, calculated by the Simpson and Teichholz method, of 25%. Pharmacological treatment was changed to achieve symptom remission. Six months later the patient was hospitalised for a new episode of HF [fatigue, muscle weakness, dyspnea, ortophnea, edema and palpitations, New York Heart Association (NYHA) class III]. At the control, blood pressure (BP) was 107/57 mmHg and heart rate (HR) 70/bpm, crackles at the basal field of lungs and pretibial edema were detected. Chest X-ray confirmed cardiac dilation and pulmonary congestion. In the following 12 months, despite the optimization of the medical therapy, the patient experienced two further episodes of acute heart failure.The therapy was changed again and included a more aggressive loop diuretic therapy, β-blockers, spironolactone and ACE inhibitors (33). As no relief in symptoms of heart failure was obtained, the patient underwent – after the acquisition of informed consent – cardiac resynchronization therapy (34-36) using an epicardial approach because of angiographic evidence of right subclavian vein occlusion (37). As six-months later, no symptom relief was reported by the patient, nor an improvement in the ejection fraction detected on the echocardiogram, the patient was addressed to heart transplantation that was performed in June 2018. At the time of transplant preevaluation, the patient showed a mild muscular impairment and no respiratory involvement.

Follow-up

The intraoperative course did not reveal any complication; the postoperative course was prolonged due to transient severe respiratory failure requiring antibiotic therapy and mechanical ventilation. The invasive ventilation was withdrawn 3 days after surgery and antibiotic therapy prolonged for 20 days. As post-operative immunosuppression, the patient received cyclosporine A and everolimus. Subsequently, oral prednisone was added to maintain immunosuppression. At one month follow-up the patient showed a successful functional rehabilitation with a good performance status. Neither evidence of graft dysfunction nor progression of muscular impairment was detected after 1 and 3 months, respectively. The cardiological post-operative follow-up included evaluation of patient's clinical status and echocardiography. At 3 months follow-up, no symptoms of heart failure (e.g. breathlessness, ankle swelling and fatigue) nor clinical signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) were found and the patient's exercise tolerance was slightly improved. Transthoracic echocardiography showed normal heart size (left ventricular end-diastolic diameter – LVEDD – was 4, 2 cm) and systolic function (EF and FS were 64% and 37%, respectively) (Fig. 2). The observed enlargement of the left atrium is a normal post-transplantation finding.

Discussion

Cardiac complications – as conduction system anomalies and arrhythmias – in patients suffering from Myotonic Dystrophy type 1 have been frequently described in the literature. Conversely dilated cardiomyopahy in general and end-stage cardiomyopathy in particular is

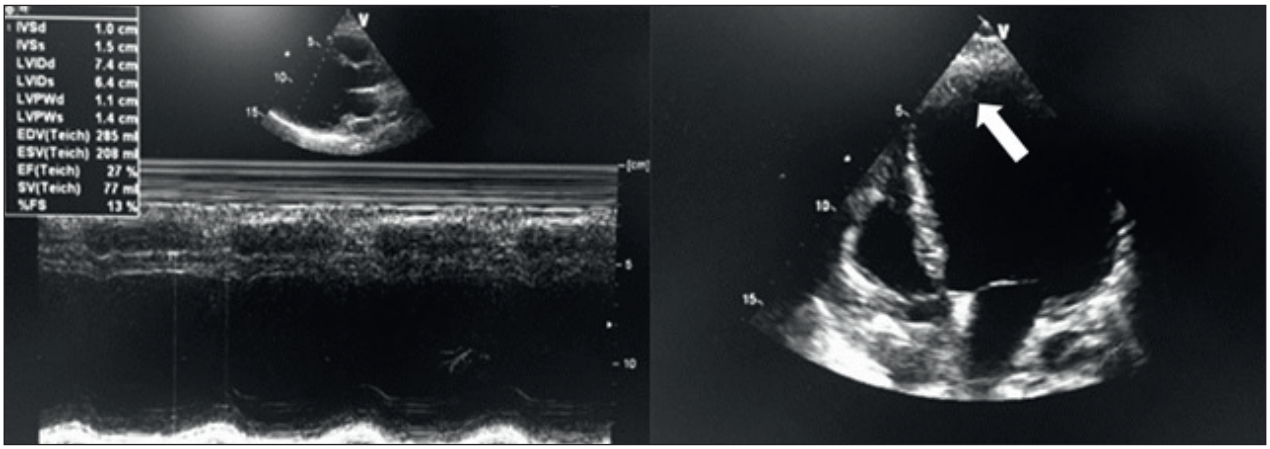

Figure 1. Echocardiographic findings six months after ICD-CRT implantation. Epicardial resynchronization therapy did not induce improvement in left ventricular ejection fraction and reverse remodeling. Please note a blood clot (thrombus) in the left apical ventricle (white arrow).

uncommon (8). The clinical recognition of congestive heart failure in muscular diseases has some more difficulties, as fatigue is often inherent to muscle weakness while exercise tolerance can be impaired by the muscle disease itself. In the classic clinical picture of myotonic dystrophy, skeletal muscle impairment appears years before the onset of cardiac symptoms. Nevertheless, in some cases, cardiomyopathy may represent the initial and unique manifestation of the inherited myopathy (4, 5), as it happened in our patient, in which a marked discrepancy between skeletal muscle and cardiac involvement was observed. In fact, while myopathy was mild and slowly progressive, cardiomyopathy displayed a rapid and severe course requiring HT about 15 years after the diagnosis.

The early onset of heart failure in this patient could be related to the electromechanical delay caused by the intra- and inter-ventricular asynchrony induced by the chronic right apical pacing that causes an uncoordination in the heart contraction which in turn accelerates the progression of the heart failure, as previously reported (37).

Heart transplantation is an elective treatment in patients with ischemic disease and refractary end-stage HF; it is usually accepted that this procedure significantly increases survival, exercise capacity and quality of life compared with conventional treatment (6). However controlled trials are not available.

Inherited myopathies in patients with endstage cardiomyopathies have always been considered a relative controindication for HT (39) because of the perioperative risk secondary to respiratory muscle weakness. Furthermore, a possible progression of the underlying myopathy due to immunosuppressive therapy, is a potential side effect with unknown consequences on the quality of life and prognosis. However, previous papers showed that clinical outcomes of cardiac transplantation in Duchenne/Becker patients with end-stage dystrophinopathic cardiomyopathy seem to be similar to a matched cohort of patients undergoing transplantation for idiopathic dilated cardiomyopathy (40-43). In particular, Cripe et al. (42) reported the case of a 14-year-old patient with intermediate Duchenne Muscular Dystrophy (IDMD), preserved pulmonary function and severe dilated cardiomyopathy who underwent successful cardiac transplantation and survived four years later. Rees et al. (43) described heart transplantation in 3 patients with DMD with a mean duration of follow-up of 40 months. All patients tolerated immunosuppression, had no complications in post-operative intubation and were able to be rehabilitated.

In our experience (40) on 4 patients with end-stage dystrophinopathic cardiomyopathy (3 Becker patients and 1 with X-linked dilated cardiomyopathy), the outcomes were without complications both in the post-operative follow-up and in the long-term follow-up.

These experiences suggest that cardiac transplantation can be successfully performed in patients with muscular dystrophy in general and in patients with Steinert disease, who present a severe cardiomyopathy, provided that they have a preserved pulmonary function and a mild muscle impairment. However, reports on clinical outcomes of cardiac transplantation in patients with muscular dystrophies or extended follow-up periods are still rare and are advisable. At our knowledge, this the second case of heart transplantation, described in literature, in a patient with Steinert disease, after that reported by Conraads et al., in 2002 (44), with satisfactory short-term results.

This case report reinforces the increasing opinon that patients with muscular disorders should have the opportunity to access cardiac transplantation because of under-

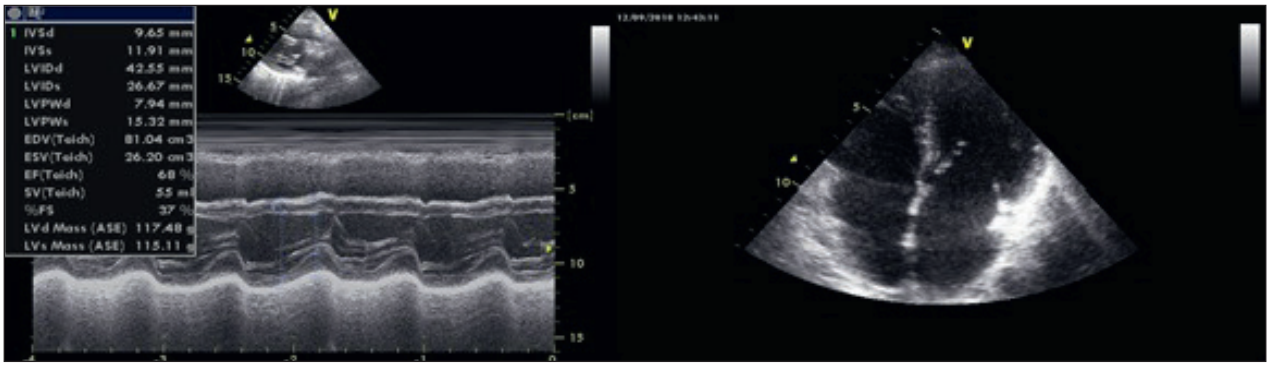

Figure 2. Echocardiographic findings 3-month after heart transplantation. The apical view and M-mode scan of the left ventricle derived from two-dimensional parasternal long axis view show a normal ventricular cavitary diameters and ventricular systolic function.

lying myopathy, as long as there is a careful selection of patients especially with regard to muscle and respiratory function.

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