Desmin – related restrictive cardiomyopathy (RCD code: III-3E)

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Abstract

Desmin – related myopathy is a chronic neuromuscular disorder caused by a mutation of desmin, an intermediate filament of the myocardial, skeletal, and smooth muscles. Clinical manifestations include skeletal myopathy, cardiac abnormalities, conduction disorders, or various types of arrhythmias. We present a case of a 33-year-old male with an end – stage restrictive cardiomyopathy and peripheral muscles myopathy caused by desmin mutation. JRCD 2013; 1 (5): 20–24

Key words: desminopathy, heart failure, myopathy, desmin mutation

Background

Restrictive cardiomyopathy (RCM) is an uncommon form of congestive heart failure (HF) of heterogeneous origin, in which diastolic dysfunction of one or both ventricles is the main pathophysiological feature [1]. Desmin-related myopathy (DRM) is a genetic skeletal and cardiac muscle disorder, caused by a mutation of the desmin gene (DES) [2]. The phenotype of desmin-related cardiomyopathy is characterized by a variable degree of neurological and cardiac involvement [3]. The course of DRM varies but inevitably leads to premature death [4].

Case presentation

A 33-year-old man with signs of chronic HF and the history of several episodes of severe cardiopulmonary decompensation was admitted to the Centre for Rare Cardiovascular Diseases at the John Paul II Hospital in Krakow, Poland, for cardiac evaluation in March 2012. He had been physically active until cardiac disorder was first diagnosed in 2007 after an acute HF episode. RCM was initially suspected on the basis of cardiac echocardiography. Subsequent coronary angiography revealed no abnormalities in the coronary arteries. Holter monitoring showed multiple ventricular and supraventricular extrasystoles and first-degree atrioventricular block. Unremarkable changes on cardiac magnetic resonance imaging (CMR) were found indicating possible myocarditis or arrhythmogenic right ventricular dysplasia. Follow-up CMR was scheduled after 3 months. Two months later, another decompensation occurred with an Adams–Stokes attack due to a newly developed third-degree atrioventricular block. A permanent cardiac pacemaker was subsequently implanted. On admission to the Centre in March 2012, he was hemodynamically unstable with signs of pulmonary congestion and peripheral edema with ascites. He required high doses of diuretics. Laboratory work-up showed elevated levels of N-terminal pro-B-type natriuretic peptide, liver enzymes, troponin T, creatine kinase (CK) and CK-MB, and myoglobin (Table 1). An echocardiographic evaluation revealed signs of RCM together with fluid overload and mildly decreased left ventricular ejection fraction of 40% (Table 2) (Figure 1, 2). His exercise capacity was considered poor. He walked a distance of 440 meters in the 6-minute walk test and reached 9 mL/(kg × min) of oxygen consumption in the cardiopulmonary exercise test. The patient complained of leg weakness; moreover, he had difficulty walking and had elevated levels of muscle enzymes (CK, myoglobin). He was consulted by neurologists, who confirmed the suspicion of myopathy and recommended electromyography with peripheral muscle biopsy. Peripheral muscle biopsy was preferred over endomyocardial biopsy because of cardiac wall thinning. Prior to the biopsy, the patient underwent right heart catheterization, which revealed elevated right atrial, right ventricular, and left ventricular end-diastolic pressures (14 mm Hg, 15 mm Hg, and 19 mm Hg, respectively). A severely decreased cardiac index of 1.35 mL/kg/min was also reported.
Desmin-related restrictive cardiomyopathy

A pathological examination of the biopsy confirmed the diagnosis of myopathy most probably as a form of myofibrillar myopathy (fig. 3). For a more precise diagnosis, a genetic evaluation was performed, which revealed desmin encoding gene mutation located in exon 3, chromosome 2 (c.735+1G>A). Medical treatment included high doses of diuretics: furosemide (160 mg once daily), spironolactone (100 mg once daily), torasemide, (15 mg once daily), and hydrochlorothiazide (25 mg once daily). Despite optimal medical treatment, the patient’s clinical condition was gradually deteriorating. He was consulted by a heart transplant team which decided against an urgent heart transplantation because of severe

**Table 1. Biochemical blood analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>NT-proBNP</td>
<td>4739 pg/ml [&lt;300]</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>AST: 48 U/L, ALT: 41 U/L, albumin: 28.1 g/L (35–52), INR: 1.14</td>
</tr>
<tr>
<td>hsTnT</td>
<td>0.305 ng/ml [&lt;0.014]</td>
</tr>
<tr>
<td>CK</td>
<td>239 U/L [&lt;190]</td>
</tr>
<tr>
<td>CKMB</td>
<td>36 U/L [&lt;24]</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>157 (23–72)</td>
</tr>
</tbody>
</table>

NT-proBNP – N-terminal pro-B-type natriuretic peptide, AST – aspartate transaminase; ALT – alanine transaminase, CK – creatinine kinase, CKMB – creatinine kinase MB isoenzyme, hsTnT – high sensitive troponin T

**Table 2. Echocardiographic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDd/LVSd</td>
<td>45/38 mm</td>
</tr>
<tr>
<td>IVSDd/IVSsd</td>
<td>8/10 mm</td>
</tr>
<tr>
<td>PWDd/PWSd</td>
<td>9/10 mm</td>
</tr>
<tr>
<td>RVd/(4ChV)</td>
<td>33/50 mm</td>
</tr>
<tr>
<td>LAa</td>
<td>28 cm²</td>
</tr>
<tr>
<td>RAa</td>
<td>32 cm²</td>
</tr>
<tr>
<td>LVEF</td>
<td>40%</td>
</tr>
<tr>
<td>Mitral flow</td>
<td>E: 0.81 m/s, A: 0.31 m/s – E/A: 2.6, E': 0.08 m/s – E'/E': 16</td>
</tr>
<tr>
<td>RVSP</td>
<td>22 mm Hg</td>
</tr>
<tr>
<td>IVC</td>
<td>18 mm, no respiratory collapse</td>
</tr>
</tbody>
</table>

LVDd – left ventricular diastolic diameter, LVSd – left ventricular systolic diameter, IVSDd – interventricular septum diastolic diameter, IVSsd – interventricular septum systolic diameter, PWDd – posterior wall diastolic diameter, PWSd – posterior wall systolic diameter, RVd – right ventricle diameter, 4ChV – four-chamber view, LAa – left atrium area, LVEF – left ventricular ejection fraction, RVSP – right ventricular systolic pressure, IVC – inferior vena cava

**Figure 1.** Transthoracic echocardiography. Transmitral pulse wave. Restrictive mitral flow

**Figure 2.** Transthoracic echocardiography. Apical four-chamber view. Enlargement of both atria. LV – left ventricle, RV – right ventricle, LA – left atrium, RA – right atrium; right atrial pacemaker electrode

**Figure 3.** Electron micrographic study. Cross-section of the peripheral muscle biopsy. Subsarcolemmal and intra myofibrillar electron-dense deposits. Presented with the courtesy of Beata Sikorska, MD, PhD, Department of Molecular Pathology and Neuropathology, Medical University of Lodz, Poland
peripheral muscle myopathy. He died soon after owing to further cardiopulmonary deterioration.

**Discussion**

**Classification**

RCM is an uncommon form of congestive HF with predominant dysfunction of the cardiac muscle. Diastolic dysfunction of one or both ventricles is the main pathophysiological feature of RCM [5]. Restricted ventricular filling is caused by reduced myocardial compliance, which leads to an increase in ventricular pressure with only a small increase of ventricular volume. Although ventricular systolic performance is usually intact, a mild-to-moderate decrease may be observed in the course of the disease. Wall thickness tends to be normal but in some cases may also be increased [1]. Typically, normal-size ventricles with markedly dilated atria and no signs of pericardial disease are major morphological findings.

Although, RCM represents a heterogeneous condition, it is grouped together with classic forms of cardiomyopathies according to the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases guidelines [6]. At the same time, the American Heart Association recognizes RCM as mixed genetic and nongenetic pathology, reflecting its etiological complexity [7]. Contrary to the other forms of cardiomyopathies classified according to the anatomical criteria, RCM is essentially a functional distinction. Therefore, a correct diagnosis of RCM may often cause difficulties as the restrictive physiology may be exhibited in numerous morphological variants.

Myocardial inflammation, infiltration, and fibrosis result in the development of restrictive myocardial disease [8]. These may be caused by infiltrative pathologies such as amyloidosis, sarcoidosis, storage diseases (including hemochromatosis or Fabry disease) or endomyocardial disorders (including hypereosinophilic syndrome, endomyocardial fibrosis, carcinoid heart disease, or anthracycline toxicity). Noninfiltrative pathologies may include idiopathic cardiomyopathy, scleroderma, or pseudoxanthoma elasticum. By far, RCM is secondary to systemic disorders.

**Epidemiology**

RCM appears to be one of the least common cardiomyopathies. Given the variety of causes, its true prevalence occurs to be vastly diverse. Cardiac amyloidosis accounts for the majority of RCM cases worldwide, whereas endomyocardial fibrosis predominates in tropical regions [1].

The actual epidemiology of idiopathic RCM is unclear. In a nationwide survey performed in Japanese hospitals, a crude prevalence of 0.2% per 100 000 population was reported [9]. Among 167 recipients of cardiac transplantation from Italy, RCM was diagnosed only in 0.6% [10]. There are several studies available concerning the epidemiology of RCM in pediatric population, which have reported that RCM accounts for 2% to 5% of all pediatric cardiomyopathies with a total annual incidence rate of 0.03 per 100 000 children [11–14].

**Clinical manifestations**

Clinically overt RCM may develop at any age. It has been more frequently observed in women than in men with the approximate 1.5:1 ratio [15]. Patients with RCM usually complain of gradual loss of exercise capacity and progressively worsening shortness of breath. In a retrospective study conducted by Mayo Clinic and Mayo Foundation researchers, dyspnea was present in 71% of the patients [15]. Other symptoms included edema (46%), palpitations (33%), fatigue (32%), and chest pain (22%). Jugular venous distension with positive Kussmaul’s sign was the most common physical finding (52%) followed by systolic murmur (49%), third heart sound (27%), pulmonary rales (18%), and ascites (15%). As many as one-third of the patients may present with thromboembolic complications [16].

**Diagnosis of RCM**

Electrocardiographic abnormalities are unspecific and often depend on the stage of the disease and the underlying cause. Atrial fibrillation is common, affecting up to 74% of the patients [15]. Also, nonspecific ST-T wave changes are frequent (75%). Premature ventricular and supraventricular beats, atrioventricular block, or intraventricular conduction abnormalities are observed in up to 20% of the patients.

Chest radiography reveals enlargement of the heart in most cases, with the cardiothoracic ratio exceeding 55%. Pulmonary congestion, interstitial edema, or pleural effusions are also commonly observed. Pleural calcifications typical for constrictive pericarditis are not usually seen on chest radiography [15].

Echocardiography is an elementary tool for diagnosing restrictive hemodynamics. In many cases, it may be helpful for distinguishing the initial cause of the observed restrictive physiology as well as for differentiation from constrictive pericarditis. The enlargement of both atria along with nondilated, well-contracting ventricles and Doppler signs of diastolic dysfunction are the most characteristic findings [17]. About 80% of the patients have mild-to-moderate mitral and tricuspid regurgitation. Doppler derived indices presenting a restrictive filling pattern include increased early diastolic filling velocity (E ≥1 m/s), decreased atrial filling velocity (A ≤0.5 m/s), increased E/A ratio (≥1.5) invariable during respiration, decreased deceleration time (≤150 ms), and decreased isovolumic relaxation time (≤70 ms) [18]. The evaluation of the pulmonary vein or hepatic vein flow shows lower systolic than diastolic forward flow and increased reversal of diastolic flow after atrial contraction. Additionally, tissue Doppler imaging reveals decreased early annular diastolic velocity (E ≤7 cm/s) and increased E/E’ ratio (≥15) indicating elevated left ventricular filling pressure [18].

Use of magnetic resonance imaging in patients with RCM provides valuable information regarding cardiac morphology and function. It is the gold standard for quantification of heart chambers and hemodynamics with standardized protocols [19,20]. Complementary to echocardiography and invasive studies, cardiac magnetic resonance imaging is a useful tool in assessing restrictive physiology [21–23]. Tissue characterization techniques enable to differentiate between particular types of RCM such as amyloidosis, sarcoidosis, or hemochromatosis as well as to detect signs of inflammation and fibrosis [20,21].
A hemodynamic profile obtained during cardiac catheterization typically presents with deep and rapid early diastolic decline in ventricular pressure with a rapid rise to a plateau, the so-called dip-and-plateau pattern or square root sign [1]. End-diastolic equalization or near-equalization of ventricular pressure, together with elevated pulmonary wedge and right atrial pressure, are also characteristic findings in RCM. As a consequence, a decrease in the cardiac index may be observed [15].

To determine the causative factor of observed restrictive myocardial disease, endomyocardial biopsy may be necessary. A pathological evaluation of specimens demonstrates patchy endocardial and interstitial fibrosis with increased collagen deposition and compensatory myocyte hypertrophy [24]. The presence of cosinophilic infiltrates, amyloid, or iron depositions helps establish the final diagnosis. To detect underlying diseases, immunofluorescent staining, immunohistochemical studies, and electron microscopy are often required [25].

**Desmin-related myopathy**

DRM, also called desminopathy (OMIM #601 419) belongs to a group of genetically determined myofibrillar myopathies [2]. As a chronic neuromuscular disorder, desminopathy is caused by DES mutation (OMIM *125 660). Desmin, a 53-kDa intermediate filament of the myocardial, skeletal, and smooth muscles, claps myofilibrils and the sarcolemma in the region of Z discs. This makes the contracting apparatus stable and thus enables the normal function of the sarcomere [26]. Over 50 DES mutations have been reported, the majority of which are missense mutations of autosomal dominant inheritance pattern [27]. However, several cases of de novo mutations or autosomal recessive inheritance pattern have also been described [28]. Defect of any of the four main domains results in the accumulation of insoluble subsarcolemmal and intracytoplasmic aggregates leading to myocyte death and consequent fibrotic replacement [29]. Detection of granulofilamentous material in histopathological, immunohistochemical, or electron microscopic studies of myocardial biopsy samples is considered a morphological hallmark of desminopathy [30].

Detailed epidemiology of DRM is currently unknown. The prevalence of DES mutation in a study of 116 families and 309 additional individuals with dilated cardiomyopathy was around 2% [31]. In another investigation of 35 Spanish families with myofibrillar myopathy, 11 were DES mutation carriers [32]. The age of onset typically varies between the second and fourth decade of life [4]. No major sex differences have been reported; however, male heterozygous mutation carriers might be more prone to develop cardiac manifestations [33]. Clinical manifestations include skeletal myopathy, cardiac abnormalities, conduction disorders, or various types of arrhythmias [4]. Typically, skeletal muscle involvement is most prominent in the distal parts of the lower limbs with slow progression to the proximal and upper limbs, trunk, neck, or facial muscles. The respiratory muscles may also be affected leading to respiratory failure and death [34]. In a meta-analysis conducted by van Spaendonck-Zwarts et al. [4], the signs of skeletal muscle disease were present in 74% of the patients with DES mutation. Distal muscle weakness was reported in 27% of the cases, proximal in 6%, and combined proximal and distal in 67%. The elevated levels of CK in mutation carriers were observed in 57% of the individuals, of whom 91% had less than a 4-fold increase, showing the limited availability of CK as a diagnostic marker. One-third of the patients had normal CK levels. Isolated neurological signs were present in 22% of the carriers and cardiac signs also in 22%. A combination of neurological and cardiac symptoms was observed in 50% of the cases. Cardiomyopathy was detected in half of the patients: dilated cardiomyopathy in 17%, restrictive in 12%, and hypertrophic in 6%. Around 60% of DES mutation carriers had cardiac conduction disease or arrhythmias including atrial fibrillation, premature ventricular beats, or ventricular tachycardia. Atrioventricular block was observed in up to 50% of DRM cases indicating it as an important feature of the disease. A pacemaker was implanted in all patients with conduction disorders, whereas only 4% of all patients had an implantable cardioverter-defibrillator implanted. Death was reported in 26% of the cases at a mean age of 49 years. Documented causes of death in both studies were sudden cardiac death, HF, respiratory insufficiency, chest infection, and iatrogenic complications of cardiac treatment [4].

Diagnosis of DRM requires a multidisciplinary approach. The presence of neuromuscular signs should prompt neurological investigation including a thorough physical examination, level of muscle-specific enzymes, needle electromyography, and muscle biopsy with subsequent ultrastructural evaluation [34]. Coexistence of cardiac involvement including cardiomyopathy, atrioventricular conduction disorders, or other types of arrhythmia shown on echocardiography or magnetic resonance imaging is often indicative of DRM [35]. The final diagnosis can be established based on detection of DES mutation. No specific therapy is currently available. Symptomatic treatment of HF is required. Cardioverter-defibrillator or pacemaker implantation can be life-saving. In some cases, heart transplantation may be needed although careful consideration is necessary.

**Our management strategy**

Since there is no DRM-specific therapy available, the patient was treated symptomatically according to the European Society of Cardiology guidelines for the management of HF [36]. He required high doses of diuretics. An angiotensin-converting enzyme inhibitor (ramipril, 2.5 mg once daily) and β-blocker (carvedilol, 3.125 mg twice daily) were administered. He was considered for urgent heart transplantation based on a few reports of successful transplantation in patients with inherited myopathies and end-stage cardiomyopathy, but due to severely impaired neuromuscular function he was rejected [37].

**Conclusion**

The coexistence of RCM, peripheral muscle weakness, and conduction disorders, especially atrioventricular block, must prompt investigation towards DRM. A thorough multidisciplinary evaluation by a neurologist, cardiologist, surgeon, pathologist, and geneticist, is necessary to determine the proper management of these patients.
References