Overlap cardiomyopathy – coexistence of hypertrophic and restrictive cardiomyopathy phenotypes in one patient (RCD code: III-2A.1)

Paweł Rubiś*, Sylwia Wiśniowska-Śmiałek¹, Lucyna Rudnicka-Sosin², Małgorzata Urbańczyk-Zawadzka³, Agata Leśniak-Sobelga¹, Magdalena Kostkiewcz¹, Maria Olszowska¹, Piotr Podolec¹

¹ Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Centre for Rare Cardiovascular Diseases, John Paul II Hospital, Krakow, Poland; ² Department of Pathology, John Paul II Hospital, Krakow, Poland; ³ Department of Cardiac Imaging, John Paul II Hospital, Krakow, Poland

Abstract

Recent data indicate that substantial proportion of cardiomyopathy patients have in fact more than one phenotype, the phenomenon termed as overlap or mixed cardiomyopathy. The molecular mechanisms and pathology as well as clinical management and prognosis of overlap cardiomyopathy is largely unknown and speculative. We report the case of 51-year-old man who was admitted due to progressive intolerance of physical activity with concomitant shortness of breath. He underwent complex cardiological studies, including invasive examinations and endomyocardial biopsy. However, despite exhaustive diagnostic work-up, the final diagnosis is still not one-hundred percent certain, and we eventually diagnosed him with overlap cardiomyopathy as most probably two phenotypes of hypertrophic and restrictive cardiomyopathy coexist. Perhaps, cardiomyopathies are far too complex entities to be easily labeled with one or another term. Accumulated data on the clinical course of various cardiomyopathies provide numerous evidence on the continuum rather than once-forever diagnosis. JRCD 2014; 1 (6): 21–28

Key words: overlap cardiomyopathy, hypertrophic, restrictive cardiomyopathy, phenotype

Introduction

Based on the specific morphological and functional features, cardiomyopathies have been traditionally grouped into four major phenotypes, namely hypertrophic (HCM), dilated (DCM), restrictive (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) [1]. Although being clinically useful, such a clear-cut distinction carries inherent flaws and occasionally may be inaccurate. Recent data indicate that substantial proportion of cardiomyopathy patients have in fact more than one phenotype, the phenomenon termed as overlap or mixed cardiomyopathy [2]. Furthermore, cardiomyopathies can also coexist with channelopathies. It seems apparent that the latter situation is even more common. Moreover, it is not uncommon to find different cardiomyopathy phenotype in the same family [3]. The molecular mechanisms and pathology as well as clinical management and prognosis of overlap cardiomyopathy is largely unknown and speculative. This is just a reflection of the complexity and incomplete knowledge on cardiomyopathies that has only recently been fully appreciated.

Case report

We report the case of 51-year-old man who was admitted due to progressive intolerance of physical activity with concomitant shortness of breath for at least six months. Patient has been professionally active and was working as a crane navigator. From his early ages he presented with severe spinal column deformation with abnormal protrusion of the right shoulder. He underwent detailed orthopedic diagnostic process as a pediatric patient, and inborn, multilevel scoliosis with axial rotation was confirmed. Despite exhaustive diagnostic work-up the etiology and pathogenesis of the spinal column deformation remained unknown.

Conflict of interest: none declared.

* Corresponding author: Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University Medical College, Centre for Rare Cardiovascular Diseases, John Paul II Hospital, Krakow, Poland; tel. 0048 12 614 22 87, fax 0048 12 423 43 76; e-mail: pawelrub@poczta.onet.pl

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In the age of 35 years he was diagnosed with paroxysmal atrial fibrillation (AF) during the routine testing by his occupational physician. His initial echocardiogram showed asymmetric left ventricular (LV) hypertrophy with preserved global contractility and ejection fraction of 72%. Additionally, enlarged left atrium was described. Being asymptomatic at that time, the patient remained under occasional check-ups during next few years. Approximately five years ago paroxysmal AF became permanent and the patient was regularly started on oral vitamin K antagonist (Acenocumarol), beta-blocker (carvedilol), angiotensin converting enzyme inhibitor (ramipril), loop diuretic (torasemide), and spironolactone. Nevertheless, he has been constantly complaining about progressive decline of physical activity tolerance and occasional shortness of breath during normal daily activities for last three years.

At presentation, besides reduced exercise capacity, patient reported paresthesia especially of upper extremities. His family history was unremarkable. Physical examination revealed irregular heart rate of 80–90 bpm, normal blood pressure of 120/80 mmHg, on-air oxygen saturation was 97%. His respiratory rate was 12/min, and normal alveolar sounds on lungs auscultation were heard. He did not present with any peripheral edemas and did not have any neurological deficits. Remarkably, his upright posture was incorrect due to aforementioned severe deformation of the spinal column.

Basic biochemical parameters, such as blood morphology, liver and kidney function tests, proteinogram and C-reactive protein level were normal but NT-proBNP was significantly elevated to 1493 pg/ml. The protrombine index PT-INR was 2.38 (on oral anticoagulation).

12-lead ECG revealed AF with ventricular response of 70–80/min, right axis deviation, deep S waves in leads V2-V3, and negative T waves in III, aVF (Figure 1 and 2).
24–hours Holter monitoring showed AF with average HR of 80/min, not significant ventricular arrhythmias, and normal circadian twenty-four-hour cycle.

An echocardiogram showed significantly dilated left and right atrium (Figure 3) that dominated over relatively small but normal sized ventricles, asymmetric LV hypertrophy (Spirito index – 3 points, Wigle index – 1 point) (Figure 4 and 5), and moderately impaired systolic function with ejection fraction of 45%. Moreover reduced diastolic volume of LV was observed. Of note, neither at rest nor at provocation LV outflow tract (LVOT) obstruction was observed. However, diastolic function was significantly impaired and non-invasive estimation of LV filling pressure was elevated (E/E’ ratio of 17). Additionally, mild-to-moderate mitral, pulmonary and tricuspid regurgitation were observed.

X-ray of the spinal column confirmed severe deformation with the dextro-scoliosis of thoracic segment, sinistro-scoliosis of the lumbo-sacralis segment with axial rotation of the vertebral column and multilevel dyscopathy (Figure 6).

In cardiopulmonary exercise test patient demonstrated very low tolerance of physical activity (peak load 3.5 METs) with peak oxygen consumption of only 12.3 ml/kg/min, that represents only 40% of referenced values for age and gender. Moreover, VE/VCO₂ ratio was also significantly elevated to 45.

Cardiac magnetic resonance imaging (CMR) confirmed significant enlargement of both atrias, particularly the left one, and asymmetric, hypertrophied LV with maximal wall thickness of 17 mm (Figure 7). Moreover it revealed non-ischemic, permanent injury.
of myocardium with numerous intramural and sub-endocardial gadolinium late enhancement (LGE) areas. (Figure 8, 9). Based on LGE pattern infiltrative or storage disease could not be excluded.

Invasive studies – coronarography and right heart catheterization (Figure 10) have been also conducted. Angiography of epicardial coronary arteries did not reveal sclerosis or any other abnormalities. However, right heart catheterization (RHC) proved significant decrease of systolic and diastolic function of the LV with highly elevated filling pressure (pulmonary capillary wedge pressure – PCWP) was estimated approximately 20 mmHg. Haemodynamic parameters of pulmonary circulation were within normal limits.

Endomyocardial biopsy from the right intraventricular septum revealed mild myocyte hypertrophy with focal disorganisation of the myocytes. Additional staining with Kongo red and Prussian blue excluded amyloid and hemosiderin deposits in the specimens. Moreover, there were diffuse myocardial fibrosis and vacuolisation of myocytes. However, inflammatory cells were not detected and small vessels were without any pathologic changes (Figure 11, 12).

**Management**

In comprehensive analysis we included patient’s symptoms, physical examination, family history and results of additional studies, such as an electrocardiogram, echocardiogram, laboratory findings, Holter-ECG, invasive procedures: coronarography and right catheterization, CMR and microscopic findings. In order to achieve a clinical improvement of our patient, we optimized the dosage of beta-blocker to obtain optimal ventricular rhythm control. Additionally the dosages of angiotensin-converting enzyme inhibitor (ramipril) and loop diuretic (torasemide) were up-titrated. At present, patient does not require implantation of cardiovert-
er—defibrillator (ICD) as a primary prevention of sudden cardiac death, as he did not complain about any faints/losses of consciousness/black-outs, and also did not have any significant ventricular arrhythmia in 24-hour ECG monitoring.

We also performed an echocardiogram of his son, as a screening of relatives, and did not find any abnormalities. Nevertheless, he and his son will stay under our observation and will be systematically examined. Furthermore, patient was encouraged to perform low to moderate recreational exercise.

**Overlap cardiomyopathy**

Although occasionally observed in a daily practice, coexistence of two or more cardiomyopathy phenotypes has not been a subject of teaching in the classical cardiology reference books. Therefore, it is important to realize the scope of the problem.

**Overlap of cardiomyopathy and channelopathy**

Coexistence of cardiomyopathy and channelopathy, a functional cardiac disorder, has been much better characterized in the literature than coexistence of two distinct forms of cardiomyopathy. Both DCM and ARVC can coexist with a mutation of ryanodine gene (RyR2) that causes catecholaminergic polymorphic ventricular tachycardia [4, 5]. Long QT syndrome type 7 or Andersen-Tawil syndrome is frequently related to LV systolic dysfunction [6]. Another variant of long QT syndrome (LQTS 8), also known as Timothy syndrome, is associated with HCM [7]. In another study it was found that small proportion, approximately 2.6%, of DCM patients have mutations in SCN5A gene [8]. Moreover, in Brugada syndrome there are numerous morphologic abnormalities, such as microaneurysms, fibro-fatty replacement, subtle cytoplasmic changes both in LV and right ventricle (RV), the significance of which is unknown [9].

**Overlap of cardiomyopathy phenotypes**

The data on the coexistence of more than one cardiomyopathy phenotype are far less accurate. Probably, LV non-compaction (LVNC) is the commonest findings among patients with other primary cardiomyopathies, e.g. almost one-quarter of DCM patients meet echocardiographic criteria for LVNC [2]. In the recent study coming from Spain, it was found that up to 13% of patients have mixed cardiomyopathy phenotypes. Individuals with DCM had most frequently observed other cardiomyopathies, such as LVNC in 31%, HCM in 1.4%, and ARVC in 0.6%. In ARVC features of DCM were observed in 13.2%, HCM in 3.9% and LVNC in 2.6%. Patients with HCM had least commonly observed overlap phenotypes, nevertheless, 1.3% had LVNC, 1.2% had DCM and only 0.1% ARVC. Another, intriguing finding of this study is coexistence between cardiomyopathies and other cardiac conditions, such as atrial or ventricular septal defects, particularly common in LVNC as well as accessory conduction pathways [3]. This is in line with the recent report from our group on the coexistence...
between LVNC, dextroposition and superior vena cava draining to coronary sinus [10].

Our patient – features of hypertrophic and restrictive cardiomyopathy

Clinical definition of HCM requires a hypertrophied, non-dilated LV without evidence of any other cardiac or systemic disease. Maximal wall thickness ≥ 15 mm is classically used as a diagnostic criterion, and hypertrophy is typically asymmetric and involves the anterior ventricular septum [11]. HCM is a disease entity caused by an autosomal dominant mutations in genes encoding contractile proteins of the cardiac sarcomere [12]. At present, eleven mutant genes are associated with HCM, most commonly β-myosin heavy chain and myosin binding protein C. In less than 10% of patients with echocardiographic phenotype of HCM, the disease is associated with other disorders, including infiltrative, metabolic, systemic, mitochondrial, and syndromic HCM [1, 11].

RCM is an uncommon, heterogeneous group of heart muscle disorders that is characterized with an impaired ventricular filling, with normal or even decreased ventricular volumes. This leads to advanced diastolic dysfunction with relative preservation of systolic function [1]. Depending on the underlying etiology, ventricular wall thickness may be normal or increased. Atrias are usually severely dilated due to increased ventricular resistance they constantly face in each diastole. The precise epidemiology of RCM is unknown but true RCM is a rare disease. Importantly, RCM is a diagnosis of exclusion because restrictive physiology is typically observed in numerous other cardiac disorders, including end-stage HCM or early stages of DCM [13]. The majority of RCM are secondary to systemic disorders, such as amyloidosis, sarcoidosis, scleroderma, haemochromatosis, eosinophilic heart disease, or as a result of radiation therapy [14].

Following the guidelines from the ESC Working Group on Myocardial and Pericardial Diseases we performed a diagnostic work-up to establish the final diagnosis. It is of paramount importance to distinguish between true HCM, caused by sarcomeric protein mutations, from the phenocopies, e.g. LVH caused by interstitial or intracellular accumulation of metabolic substrates. The scope of the detailed analysis include symptoms and physical examination, family history, electrocardiogram, echocardiogram, laboratory findings, CMR, and microscopic findings.

Symptoms and clinical examination

Our patient mostly complained about progressive impairment of exercise capacity, which was objectively confirmed in cardiopulmonary exercise test. Although majority of HCM patients complain about various degree of exercise intolerance, nevertheless, the magnitude of physical impairment was remarkably high in our patient and was rather characteristic for end-stage HCM or some other cardiac condition. Apart from this patient occasionally complained about paresthesia, which is typical for Fabry disease or amyloidosis. Moreover, he has severe deformation of the spinal column, the nature of which is unknown yet and definitely contributes to low physical tolerance. Of note, he did not have peripheral muscle weakness.

Summary: patient's symptoms are rather untypical for HCM and such severe functional intolerance was rather characteristic for RCM or serious systemic condition.
**Family history**

In great majority of cases, HCM is inherited as an autosomal dominant trait with incomplete penetrance and variable expression. Therefore, the detailed pedigree analysis is mandatory. However, family history was unremarkable in our patient. Importantly, a ‘negative’ family history does not exclude a genetic etiology because the disease may be result of de novo mutations or more frequently an unrecognized myocardial disease in the family.

Summary: patient’s family history was unremarkable and this should be viewed as a neutral finding.

**Electrocardiogram**

Main feature of our patient’s ECG is a permanent AF with adequate ventricular rate control. Interestingly, patient has a long history of AF as it appeared for the first time when he was 35 years old. AF is common both in HCM and RCM. The search for other concomitant ECG abnormalities, such as atrio-ventricular block, extreme LVH, low QRS voltage or extreme superior QRS axis deviation, typically observed in infiltrative LVH was negative.

Summary: the onset of AF was long before the diagnosis of cardiomyopathy, and is rather a neutral finding.

**Echocardiography**

Echocardiography is the first line imaging tool for all forms of heart muscle diseases. Furthermore, based on the main echocardiographic phenotype, patients with cardiomyopathy are allocated to four major groups. In fact, this is echocardiographic examination that initially has raised suspicion of overlap cardiomyopathy in our patient. Intriguingly, we found mild concentric LV hypertrophy and after exclusion of long-lasting arterial hypertension and endurance sport (athlete heart), the working diagnosis of HCM seemed to be quite natural. Although LV systolic function was mildly depressed to approximately 45%, still it is not uncommon. What was unusual or a ‘red flag’ was the global appearance of the heart with grossly dilated atrias that dominated relatively small ventricles. At this stage, we had a diagnostic clue of possible RCM or a mixed phenotype. As the patient was in AF, the state-of-the-art assessment of diastolic function was imperfect, nevertheless, high velocity mitral E-wave and low myocardial E’ velocity, causing high E/E’ ratio, indicated severely depressed diastolic function. Obviously, some degree of diastolic dysfunction is typical for HCM as well, however, the magnitude of observed diastolic abnormalities strongly suggested restrictive physiology. The assessment of RV morphology and function as well as assessment of pulmonary hemodynamics did not provide any additional information. Likewise, no obvious ground-glass appearance or double-layered of ventricular myocardium was observed.

Summary: at this stage it was obvious that the patient did not have a typical HCM and in order to facilitate diagnosis we had to move towards CMR and possibly endomyocardial biopsy.

**Laboratory findings**

First level laboratory examination, including creatine phosphokinase (CK), renal and liver function tests, proteinuria, haemoglobin and white blood cell count, serum iron and ferritin did not reveal any abnormalities. Similarly, second level examinations, such as alpha-galactosidase A level (screening for Anderson-Fabry disease), arterial blood gases and measurements of lactic acid (screening for mitochondrial diseases), serum immunoglobulin free light chains (diagnosis of AL amyloidosis) also proved negative. Of note, NT-proBNP level was significantly elevated to 1493 pg/ml (UNL <125 pg/ml).

Summary: apart from conformation of increased myocardial strain (significant elevation of natriuretic peptide), no other significant blood changes were found.

**Cardiac magnetic resonance**

CMR is a valuable examination in the assessment of cardiomyopathies. Abnormal CMR findings may relate to myocardial edema, fatty replacement, iron storage, amyloid infiltration, and myocardial fibrosis. CMR in HCM is particularly useful in the detection of early disease expression, detailed characterization of established diseases, and distinguishing phenocopies. Similarly, CMR in RCM enables to detect myocardial infiltration and pleural/pericardial effusions (clues to amyloid) or specific late gadolinium enhancement (LGE) pattern or hilar lymphadenopathy (sarcoid). In our patient CMR revealed normal size and volume of LV, gross enlargement of both atrias, mild-to-moderate myocardial hypertrophy, particularly in interventricular septum and lateral wall, and numerous mid-myocardial and sub-epicardial LGE-positive areas. Of note, there were no signs of myocardial inflammation. Gadolinium enhanced CMR is particularly useful to detect expansion of the myocardial interstitium caused by inflammation, fibrosis, or extra-cellular deposition of proteins. Therefore, excluding active inflammation, LGE areas represent either fibrosis or extra-cellular matrix infiltration, both of which are frequently observed in HCM and RCM.

Summary: based on CMR findings it is still impossible to distinguish HCM from RCM as CMR features are characteristic for both phenotypes.

**Invasive studies – coronaryography**

There were no signs of atherosclerosis in coronary arteries. Of note, circumflex artery originated from proximal part of right coronary artery.

**Right heart catherization**

RHC revealed severely decreased cardiac output, moderate elevation of pulmonary capillary wedge pressure and mean pulmonary pressure in the upper normal limit (24 mmHg) alongside with...
normal pulmonary vascular resistance (2.6 Wood units). Importantly, characteristic ‘dip-and-plateau or square root sign’ were found in ventricular pressure tracings, that represent deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to plateau in early diastole – the pathognomonic sign of RCM. Furthermore, such a severe impairment of LV systolic function is another feature of RCM.

Summary: the results of RHC are very characteristic for RCM.

## Endomyocardial biopsy

EMB was performed via right femoral vein from the RV inter-ventricular septum. Histopathologic assessment of myocardial samples revealed mild myocyte hypertrophy with focal disorganisation of the myocytes (cardiomyocyte disarray). Special staining with Kongo red and Prussian blue excluded amyloid and hemosiderin deposits in the specimens.

Summary: the main findings of EMB were myocyte hypertrophy and disarray (in favor of HCM but does not exclude RCM) and focal areas of fibrosis, that are frequently observed in both HCM and RCM.

## What is the final diagnosis then?

Despite exhaustive and accurate diagnostic work-up, the final diagnosis is still unclear. It is hard to imagine any more tests that could have helped to establish diagnosis with one-hundred percent certainty. Even incorporating genetic testing, that is not currently available on the mass scale, would not have probably much effect as there are numerous examples of the same mutations that cause HCM in one patient and RCM in another. Perhaps, cardiomyopathies are far too complex entities to be easily labeled with one or another term. Accumulated data on the clinical course of various cardiomyopathies provide numerous evidence on the continuum rather than once-forever diagnosis. The examples that easily escape our understanding, such as transition of HCM to end-stage phase that is indistinguishable from DCM or ARVC with predominant LV involvement or alcohol-induced DCM that completely reverse after abstinence and HCM without hypertrophy, can be multiplied.

The recent concept of overlap or mixed cardiomyopathies seems to be attractive. Although it is probably right from the pathologic point of view, nevertheless, could be problematic from the clinical perspective. Clinicians prefer to know what kind of disease they treat and moreover like to have their therapeutic decisions backed by the guidelines. Unfortunately, with the concept of overlap cardiomyopathy neither final diagnosis nor optimal management are precisely defined. However, one should not go into despair as cardiomyopathies are very dynamic field and sooner or later we will know the answers to many unresolved questions.

## References