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CASE REPORT

INTERMEDIATE

CLINICAL CASE

A Case of Rare Inherited Restrictive Cardiomyopathy With Severe Biatrial Enlargement

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ABSTRACT

We describe a case of inherited restrictive cardiomyopathy in a patient presenting with severe biatrial enlargement. We review the evaluation and management of restrictive cardiomyopathy with a focus on genetic etiologies. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2019;1:588–91) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 69-year-old man presented with 5 months of progressive dyspnea on exertion and volume overload. He was transferred to our hospital for medically refractory heart failure.

MEDICAL HISTORY

The patient's medical history was notable for long-standing, persistent atrial fibrillation (AF). His earliest transthoracic echocardiogram 6 years previously showed severe biatrial enlargement, normal left ventricular (LV) function with moderate concentric LV hypertrophy, normal right ventricular function, mild mitral regurgitation, and moderate to severe tricuspid regurgitation.

The patient has the following family history: AF in his mother; AF and heart failure in his father; and AF in his younger brother. He is a remote smoker (10 pack-year history). He is retired from working in historical restorations and previously served as a rescue diver for the U.S. Coast Guard.

LEARNING OBJECTIVES

- To develop a differential diagnosis and evaluation for RCM and its clinical sequelae.
- To understand the genotypic and phenotypic similarities between hereditary RCM and HCM.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the patient's heart failure symptoms included tachycardia-induced cardiomyopathy secondary to AF with primary atrial remodeling, chronic obstructive pulmonary disease with cor pulmonale, heart failure with preserved ejection fraction and secondary pulmonary hypertension, valvular heart disease, ischemic cardiomyopathy, inherited cardiomyopathy, amyloid cardiomyopathy, and other forms of restrictive cardiomyopathy (RCM).

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Informed consent was obtained for this case.

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INVESTIGATIONS

The patient's examination showed marked jugular venous distention, abdominal distention, and lower extremity edema. He was tachycardic in an irregularly irregular rhythm with holosystolic murmurs at the apex and right lower sternal border. His oxygen saturation was 91% on 3 L by nasal cannula, and his lung fields had bibasilar crackles. Basic laboratory test results were notable for an elevated creatinine level of 1.4 mg/dl and low hemoglobin level of 7.6 g/dl. His total bilirubin level was elevated at 1.8 mg/dl with normal transaminase levels, and his N-terminal pro-B-type natriuretic peptide level was elevated at 2,200 pg/ml.

The patient's electrocardiogram revealed AF with frequent premature ventricular contractions and left posterior fascicular block (**Figure 1**). His chest radiograph showed pulmonary edema and profound cardiomegaly. His transthoracic echocardiogram revealed massively enlarged left and right atria, nondilated ventricular chambers, preserved LV systolic function with moderate LV hypertrophy and grade III diastolic dysfunction, mild right ventricular dysfunction, moderate mitral regurgitation, and torrential tricuspid regurgitation (**Figure 1**, Videos 1 and 2). A saline microcavitation contrast study to assess for interatrial shunting was positive at rest, concerning for a patent foramen ovale. Cardiac magnetic resonance delayed enhancement imaging showed no evidence of myocardial infarction, scar, or infiltrative disease (e.g., amyloidosis or sarcoidosis), although single-shot imaging was used due to his inability to breath hold. The patient's intracardiac pressures on right heart catheterization were significantly elevated with a normal cardiac index of 3.3 l/min/m^2 (**Table 1**). Unfortunately, we were unsuccessful in performing an endomyocardial biopsy due to severe right atrial enlargement and severe tricuspid regurgitation.

Pulmonary function testing to assess for chronic obstructive pulmonary disease revealed a mixed obstructive and restrictive defect. A ^{99m}Technetium-pyrophosphate scan showed no evidence of transthyretin amyloidosis and no discernible myocardial uptake of radiotracer (**Figure 1**). Results of laboratory evaluation for hemochromatosis (i.e., ferritin, transferrin saturation) and inherited disorders of metabolism (i.e., acylcarnitine profile, plasma amino acids) were negative.

As part of an ongoing research protocol to determine intravascular volume status and the nature of anemia in patients with heart failure, we performed a blood volume analysis (BVA) using I^{131}-radiolabeled albumin (1). The patient's BVA revealed an extreme plasma volume excess as well as dilutional anemia based on a severe red blood cell excess (**Figure 2**).

Next-generation sequencing of a comprehensive cardiac genetic panel revealed a pathogenic missense mutation in the gene *MYBPC3* (coding deoxyribonucleic acid 1624: guanine to cytosine). It also revealed variants of unknown significance in the genes *TTN*, *GAA*, and *DSG2*.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BVA = blood volume analysis

HCM = hypertrophic cardiomyopathy

LV = left ventricular

RCM = restrictive cardiomyopathy

MANAGEMENT

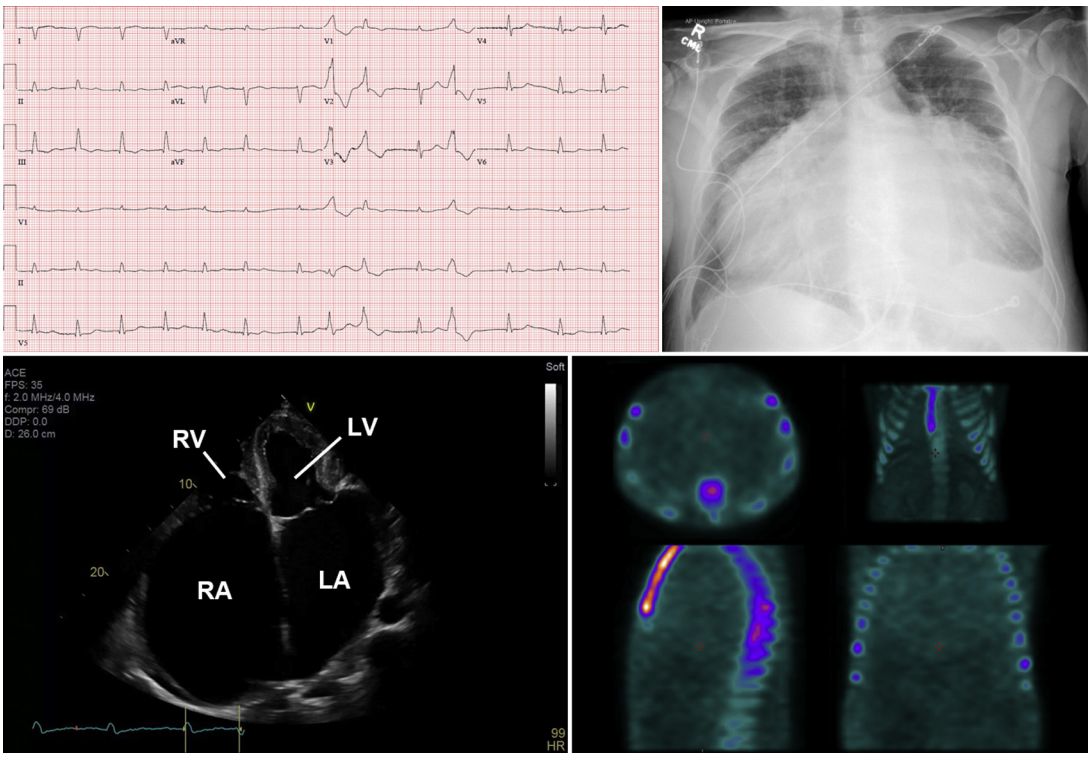
The patient underwent aggressive diuresis with furosemide infusion and metolazone, and he required low-dose inotropic support for worsening right heart failure and cardiorenal syndrome. He was anticoagulated with heparin infusion and started on amiodarone, which resulted in modest rate control of his AF. A rhythm control strategy was not pursued due to low likelihood of maintaining sinus rhythm given the patient's severe left atrial enlargement. Due to lack of effective medical stabilization and mechanical support options, he was listed for heart transplantation, and he underwent a successful transplant with an uncomplicated post-transplant course. His oxygen requirement resolved several days after his transplantation, and his acute kidney injury resolved before discharge.

DISCUSSION

Severe biatrial enlargement can be seen in RCM as a result of high atrial filling pressures and chronic remodeling. RCM, characterized by severe diastolic dysfunction secondary to increased myocardial stiffness, has a broad differential diagnosis, including infiltrative disorders (e.g., amyloidosis, sarcoidosis), storage diseases (e.g., hemochromatosis, Fabry's disease), endomyocardial disorders, and hereditary RCM (2). Hereditary RCM is caused by sarcomeric and cytoskeletal gene mutations with autosomal dominant inheritance and variable penetrance due to epigenetic and environmental factors (3,4).

The patient carried a missense mutation in the gene encoding myosin-binding protein-C, which is involved in sarcomere formation, organization, and function. Mutations in *MYBPC3* can cause hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, and RCM (4,5). Although the mutation this patient carried (*MYBPC3*:c.1624G>C) has been reported to be causative in HCM, it has not been

FIGURE 1 Representative Clinical Data



(Upper left panel) Electrocardiogram showing atrial fibrillation with frequent premature ventricular contractions. **(Upper right panel)** Chest radiograph showing pulmonary edema and profound cardiomegaly. **(Lower left panel)** Still frame from transthoracic echocardiogram apical 4-chamber view showing massively enlarged left and right atria. **(Lower right panel)** ^{99m}Technetium-pyrophosphate scan showing no myocardial uptake of radiotracer. See Videos 1 and 2. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

reported to cause RCM (6). Pathological analysis of his explanted heart showed biventricular hypertrophy (LV posterior wall thickness of 1.4 cm, septal wall thickness of 1.5 cm, and right ventricular wall thickness of 0.7 cm), as well as myocyte hypertrophy and mild focal myocyte disarray on histology, which can be seen in both HCM and hereditary RCM. Taken together, the patient's clinical presentation highlights the overlap between these 2 hereditary disorders and emphasizes the value of genetic testing in idiopathic RCM to improve genotype-phenotype correlations. Moreover, genetic testing in cases with a high index of suspicion for disease inheritance should be considered to help identify at-risk family members and avoid delays in diagnosis and treatment (7).

TABLE 1 Right Heart Catheterization Pressures

	Systolic (mm Hg)	Diastolic (mm Hg)	EDP (mm Hg)	Mean (mm Hg)
Aorta (cuff)	106	62	–	77
Right atrium	–	–	–	23
Right ventricle	44	15	22	
Pulmonary artery	42	27	–	33
Pulmonary capillary wedge	–	–	–	27

EDP = end-diastolic pressure.

Management of RCM, as with other forms of diastolic heart failure, involves optimizing volume status with diuretic agents. Notably, the patient's BVA revealed massive intravascular plasma volume expansion. AF is commonly associated with RCM and warrants systemic anticoagulation. Heart transplantation should be considered for suitable candidates with American College of Cardiology/American Heart Association Stage D heart failure from RCM (8).

FOLLOW-UP

The patient did well after cardiac transplantation, with significant improvement in symptoms and

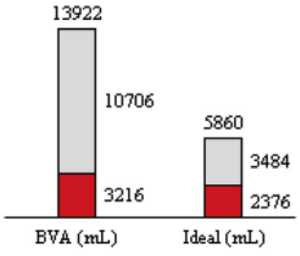
FIGURE 2 **BVA Results**

Blood Volume Analysis Results

	BVA Result	Patient Ideal	Deviation From Ideal	Excess/Deficit %
Total Blood Volume	13922 mL	5860 mL	+8062 mL	+137.6% Extreme Excess
Red Blood Cell Volume	3216 mL	2376 mL	+840 mL	+35.4% Severe Excess
Plasma Volume	10706 mL	3484 mL	+7222 mL	+207.3% Extreme Excess

Blood Volume Interpretation Guideline

	Normal	Mild	Moderate	Severe	Extreme
BV, PV Deviation (± %):	0 to 8	>8 to 16	>16 to 24	>24 to 32	>32
RCV Deviation (± %):	0 to 10	>10 to 20	>20 to 30	>30 to 40	>40



Blood volume analysis (BVA) using I^{131}-radiolabeled albumin showing an extreme plasma volume excess and severe red blood cell excess. BV = blood volume; PV = plasma volume; RCV = red blood cell volume.

functional capacity. Results of his latest heart biopsy show no evidence of rejection. He has been referred for follow-up in our Genetics Clinic. We have recommended genetic screening for his first-degree relatives, including a 35-year-old son and 10-year-old daughter.

CONCLUSIONS

The authors present a case of inherited RCM caused by an *MYBPC3* mutation in a patient with severe biatrial enlargement and rapid symptom progression who ultimately underwent a successful heart transplantation. The evaluation of RCM requires an understanding of its varied etiologies. Genetic testing for hereditary RCM should be considered when secondary causes have been excluded. Select patients with end-stage RCM may be referred for evaluation for heart transplantation.

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KEY WORDS cardiac transplant, cardiomyopathy, imaging, genetic disorders, restrictive

APPENDIX For supplemental videos, please see the online version of this paper.