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## Case Report

## A case of restrictive cardiomyopathy complicated by recurrent pulmonary thromboembolism originating at the right atrial appendage



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## ABSTRACT

Idiopathic restrictive cardiomyopathy (RCM) is rare, and its natural history is not well known. Its prognosis in infants is extremely poor, whereas patients with RCM occurring in middle age have comparatively good prognoses. Here, we report a case of idiopathic RCM with the disease onset at 10 years old. Echocardiography and cardiac catheterization revealed a biventricular restrictive pattern; however, the right ventricle showed more severe restriction. At 20 years old, severe pulmonary thromboembolism (PTE) occurred with circulatory collapse. The right atrium was extremely enlarged and the appendage was filled with moderate thrombi that migrated to pulmonary arteries. PTE is a rare complication of idiopathic RCM; however, this complication occurs more commonly in other secondary RCMs. In patients with restrictive hemodynamic pattern, the presence of thrombi in cardiac cavities should be routinely examined.

<Learning objective: A patient with idiopathic restrictive cardiomyopathy, with disease onset at 10 years old, is described. Echocardiography and cardiac catheterization revealed biventricular restrictive pattern, however right ventricle showed more severe restriction. At 20 years old, he had severe pulmonary thromboembolism. The right atrial appendage was filled with moderate thrombi that migrated to pulmonary arteries. The right atrium should be assessed to determine the presence of thrombi in patients with restrictive hemodynamic pattern.>

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## Introduction

In the 2008 statement of the European Society of Cardiology [1], restrictive cardiomyopathy (RCM) is classified as one of the five major cardiomyopathies. However, this cardiomyopathy is extremely rare in comparison with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy. In 2016, the Japanese registry of patients with RCM included only 50 persons [2]. Thus, the genetic background remains to be elucidated. A representative gene, *TNNI3*, encodes the protein troponin I; its defects are thought

to be related to poor prognosis in young patients [3]. The clinical course of RCM is also not well known. In children with RCM, the prognosis is extremely poor with the 5-year survival rate of 39% [3]. Many infants with RCM require heart transplantation. In contrast, patients with RCM that developed in middle age have comparatively good prognoses, although their 5-year survival rate is approximately 60% [4,5].

In our case, RCM was diagnosed at 12 years old, and complicated by recurrent pulmonary thromboembolism (PTE) during the 16-year follow-up period.

## Case report

A male patient first demonstrated abnormalities on electrocardiography (ECG) at 10 years old. During heart screening for school

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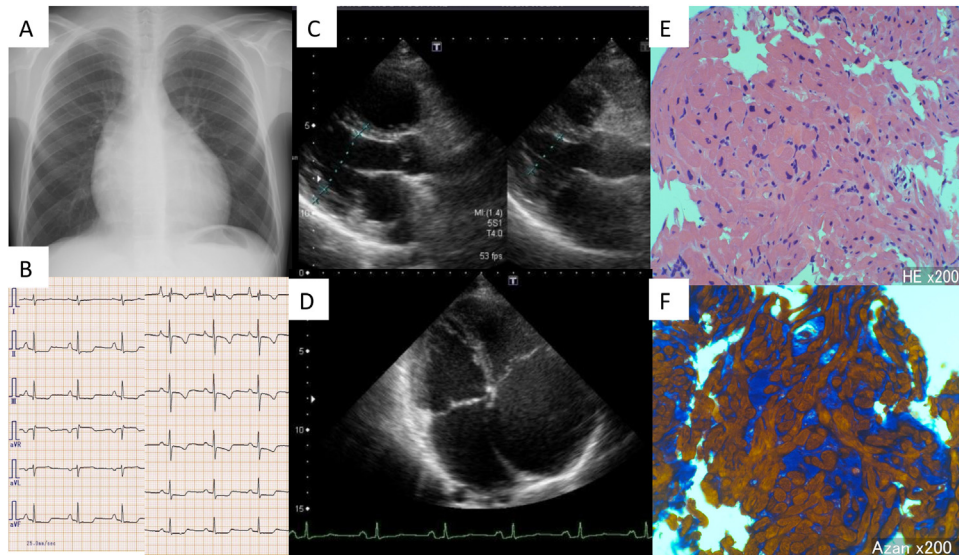


Fig. 1.

Various examinations were performed at 13 years old. (A) Chest X-ray showed a cardiothoracic ratio of 54% without pulmonary congestion. (B) Twelve-lead electrocardiogram showed the prominent pulmonary P wave and ST segment depression in V2-5 and inferior leads. (C), (D) Echocardiography showed normal left ventricular systolic function and wall thickness with marked right atrial dilation. (E), (F) Cardiac biopsy sample showed disruption and disarray of cardiomyocyte columns. Interstitial fibrosis was observed moderately.

children at 12 years old, an ECG abnormality was still observed; further examination with echocardiography revealed normal systolic function of the left ventricle (LV) and right ventricle (RV) and also the impairment of biventricular diastolic function that was marked in RV (Fig. 1A–D). Measurement data are shown in Table 1, which indicated normal left ventricular ejection fraction (LVEF) of 64% and normal wall thickness. Diastolic function represented by  $E/e'$  and  $E/A$  were elevated in both ventricles and an Ar duration of 185 msec by pulmonary vein flow pattern, that was longer than an A wave duration of 116 msec by the transmitral flow, also implied LV restriction. The patient was referred to the children's hospital, where cardiac catheterization was performed. Hemodynamic data demonstrated elevated RV end-diastolic pressure (13 mmHg), and RA pressure (10 mmHg). Pressure pattern was dip and plateau in both ventricles. A cardiac biopsy sample was obtained from the RV showing disarray of cardiomyocytes, moderate interstitial fibrosis, and no amyloid substance

deposition or eosinophil accumulation (Fig. 1E and F). Considering all these findings, the patient was diagnosed with idiopathic RCM. His physicians recommended heart transplantation, but he and his family refused. His mother was suspected of RCM with normal systolic LV function and wall thickness (LVEF of 70.3% and wall thickness of 7 mm). She had enlarged biatria with mild LV hypocompliance ( $E/A$  of 3.2 and  $DcT$  of 112 ms). However, the conclusive final diagnosis was not obtained.

At 15 years old, he was admitted to the hospital due to moderate ascites, and admitted to the hospital several times thereafter due to RV failure. At 20 years old, the patient experienced common-type atrial flutter. Hence, radiofrequency ablation of the cavo-tricuspid isthmus was performed. Approximately 2 months later, he suddenly went into shock and was referred to our hospital. In the emergency room, his blood pressure was 81/44 mmHg, and he exhibited severe pallor with brain natriuretic peptide level of 515.6 pg/mL and D-dimer level of 10.2  $\mu\text{g/mL}$  (normal

Table 1

Echocardiography	Measured value; at 13 years old	Measured value; at 28 years old	Normal value (20–29 years, men)	Hemodynamics	Measured value; at 13 years old
IVST, mm	6.0	7.0	$8 \pm 1$	MPA, mmHg	16
LVPWT, mm	8.0	8.0	$8 \pm 1$	RAP, mmHg	10
LVDD, mm	40.4	45.0	$49 \pm 4$	RV, mmHg	27
LVSD, mm	26.5	29.0	$31 \pm 4$	AAO, mmHg	70/40 (55)
LVEF, %	64	66	$64 \pm 4$	LV, mmHg	70
$E/e'$ , LV sep ( $e'$ )	8.9	14.4 (2.7)	$6.3 \pm 1.6$ , $e'; 12.6 \pm 2.2$	CI, L/min/m <sup>2</sup>	2.4
$E/e'$ , LV lat ( $e'$ )	4.4	5.0 (7.8)	$4.8 \pm 1.5$ , $e'; 16.9 \pm 3.4$	LVEDV, ml	69.0
$E/e'$ , RV lat ( $e'$ )	22.3	16.0 (3.6)	$<6.0$ , $e' > 7.8$	LVEF, %	70.0
RV FAC, %		38	$46 \pm 10$	RVEF, %	60.0
$E/A$ (LV)	2.42	1.46	$2.0 \pm 0.5$		
$E/A$ (RV)	3.35	2.4	$1.4 \pm 0.6$		
$DcT$ (LV)		148	$185 \pm 34$		
Max LA volume/BSA, ml/m <sup>2</sup>		40	$24 \pm 8$		
TRPG, mmHg		10			

Normal value is cited from Daimon M Circ J 2008;72:1859–66. and Nageuh SF et al. J Am Soc Echocardiogr 2016;29:277–314.

IVST, interventricular septum thickness; LVPWT, left ventricular posterior wall thickness; LVDD, left ventricular diastolic dimension; LVSD, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; FAC, fractional area contraction;  $DcT$ , deceleration time; TRPG, tricuspid regurgitation pressure gradient; MPA, main pulmonary arterial pressure; RAP, right atrial pressure; RV, right ventricular pressure; EDP, end-diastolic pressure; AAO, ascending aortic pressure; LV, left ventricular pressure; CI, cardiac index; LVEDV, left ventricular end-diastolic volume; RVEF, right ventricular ejection fraction.

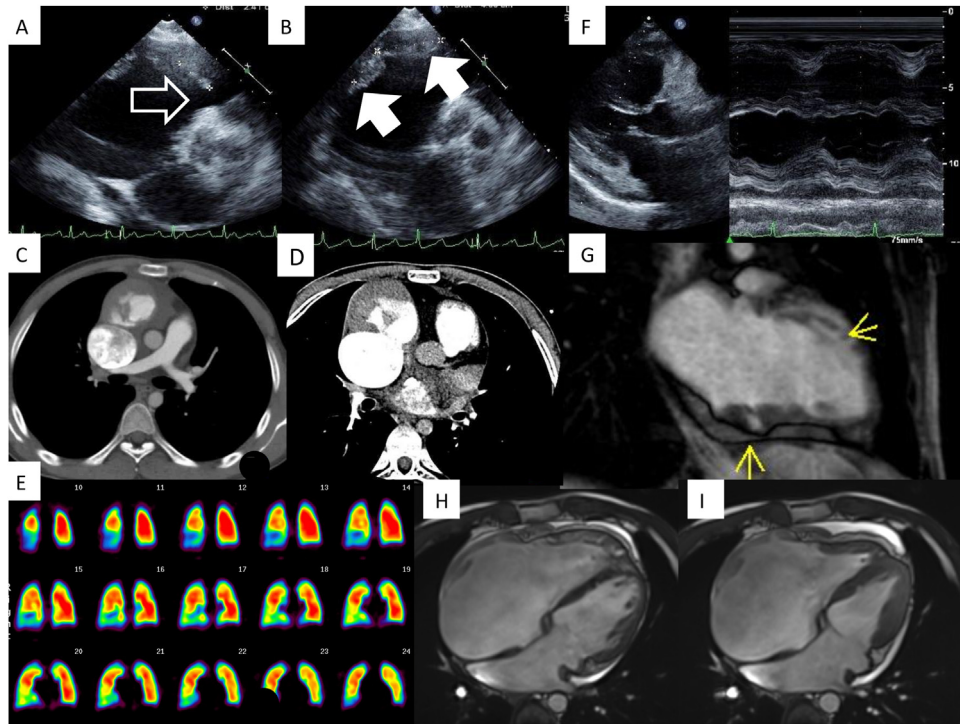


Fig. 2.

(A–E) Examinations were performed at pulmonary thromboembolism onset. (A, B) Echocardiography showed the lateral wall contained mural thrombi that are attached (white arrow) and floating thrombus (black arrow). (C, D) Computed tomography showed massive mural thrombus located mainly in the right atrium appendage with moderate right to left blood flow shunting. (E) Lung perfusion scintigram obtained approximately 2 weeks after hospital admission, showed the right inferior perfusion defects. (F–I) Examinations performed at 28 years old. (F) Echocardiography showed normal left ventricular (LV) systolic function and thickness, with enlarged left atrium (LA). Detailed data are shown in Table 1. (G) Late gadolinium enhancement of the LV showed multiple patchy defects chiefly in the middle layer. (H, I) Magnetic resonance image of cine mode. (H) End-diastole phase. (I) End-systole. Systolic function of both ventricles was not impaired and wall thickness was almost within normal limits. Right atrial enlargement was prominent, compressing the LA; however as shown in Table 1, the LA size was larger than the normal range.

range,  $<1.0 \mu\text{g/mL}$ ). Echocardiography showed large right atrial (RA) thrombi moving with the cardiac cycle (Fig. 2A and B). Computed tomography revealed RA dilatation, massive mural thrombus in the RA, especially in the appendage (Fig. 2C and D), and leftward shift of the interatrial septum. Mural thrombi were also found at the middle part of the right pulmonary artery. One week later, lung perfusion scintigraphy was performed revealing multiple defects mainly in the right lower lung (Fig. 2E), although the ventilation scan was not available. All of these findings indicated that the diagnosis was PTE originating from the mural thrombi of RA. A full-dose heparin was infused for 1 week and then switched to warfarin. As far as we have investigated, neither obvious systemic thromboembolism, nor left atrial thrombus was observed.

Four months later, he was readmitted because of almost the same complaints, although the mean value of prothrombin time-international normalized ratio during this period was 2.29. Symptom and hemodynamic changes were comparatively mild. The D-dimer level was  $3.0 \mu\text{g/mL}$ .

The patient was subsequently monitored for 8 years using warfarin without PTE recurrence. At 28 years old, he was admitted because of massive ascites, as confirmed with echocardiography and magnetic resonance. Echo images are shown in Fig. 2F and Table 1 displays various parameters: the LV wall thickness, 7–8 mm, LVEF, 66% with high E/e' value of 13.5. RV was slightly dilated with E/e' value of 9.4 and slightly reduced systolic function shown by the fractional area contraction of 27%. Late gadolinium enhanced image (Fig. 2G–I) showed multiple patchy defects in the LV mimicking HCM. However, four chamber views of the end-systole and end-diastole revealed wall thicknesses with almost

normal chamber sizes, which denied the transformation of RCM to HCM, arrhythmogenic right ventricular cardiomyopathy (ARVC), and endomyocardial fibrosis (EMF) for over 15 years.

## Discussion

RCM is a rare disease characterized by lack of cardiomegaly, lack of hypertrophy, near-normal LV systolic function, and impaired LV diastolic function. It is classified into two types: idiopathic RCM, and secondary RCM such as amyloidosis, hypereosinophilic syndrome, and EMF. The European Society of Cardiology and American Heart Association guidelines stress the importance of this clinical entity [6]; however, these RCMs are extremely rare.

Various genetic mutations, reported in patients with idiopathic RCM, are also found in patients with HCM. In HCM, the gene mutation that regulates the myosin heavy chain activity usually results in severe hypertrophy with fairly good prognosis, whereas the gene mutations that regulate troponin cause mild hypertrophy only but with poor prognosis. The coexistence of RCM and HCM phenotypes in members of the same families implies that interaction with other genes may play a role in determining the phenotype [7]. The age at disease onset is also very different from case to case. Infants with RCM have a worse prognosis and may require heart transplantation. In patients with RCM onset in middle age, the prognoses are comparatively good, but in a Korean series, the mean age was 53.2 years, with the 5-year survival rate of only 64.4% [5].

Our patient had idiopathic RCM, not secondary RCM as indicated by echocardiography, hemodynamic data, and biopsy findings. This case has special characteristics of having enlarged RA, showing RV restriction is more prominent than LV. The LV

restrictive pattern is not conspicuous but is confirmed by E/e', E/A, deceleration time, enlarged LA volume, and longer Ar duration with structural findings of patchy fibrosis shown by magnetic resonance imaging (MRI). This LV restriction usually causes pulmonary hypertension (PH). However, in our case, severe RV restriction might attenuate the elevation of pulmonary artery pressure. Constrictive pericarditis also shows biventricular restrictions without prominent PH. Regarding the differential diagnosis, RV is not that dilated and LV wall thickness is not changed during 15 years, indicating that this case is neither ARVC nor HCM. Some case reports investigated and described the RV dominant restrictive pattern that caused the ascites [8]. Such RV dominant restrictive pattern is frequently observed in EMF, especially right EMF, an endemic disease in south India and Africa. EMF shows RV apex obliteration with thrombi [9]. This case does not show EMF-like images in the MRI. All of these findings confirm that this case is diagnosed as idiopathic RCM, although this special predominance of RV diastolic dysfunction is unique. Our case seems to be familial RCM, thus these special features may be caused by special genetic mutations, although the genetic testing was not performed.

PTE is a rare complication of this rare disease. Some authors have reported PTE as a complication of RCM [10], and in cases of secondary RCM, such as EMF and hypereosinophilic syndrome, PTE and PH have been commonly described [9]. In this patient, the radiofrequency ablation of the cavo-tricuspid isthmus for the common-type atrial flutter was performed approximately 2 months before the PTE occurrence. This might have caused the formation of mural thrombi. However, the ablated area was restricted to the cavo-tricuspid isthmus, and the main source of thrombi was the right atrial appendage. Therefore, catheter ablation had only a minor, if any, influence on PTE formation.

## Conclusion

RCM is a rare disease and the patient presented here is unique because the RV restrictive pattern is more prominent than LV restrictive pattern. Our patient initially manifested idiopathic RCM at 10 years old and was complicated by severe PTE during the follow-up period. This complication is also rare; however, it can

occur more commonly in secondary RCM, especially in EMF. The occurrence of PTE as a complication of RCM should be carefully considered even in the condition without atrial fibrillation, and the presence of thrombi in cardiac cavities should be routinely examined.

## Conflict of interest

None of the authors have any conflicts of interest to disclose.

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