A case of dilated left ventricle with multiple outpouchings: A severe congenital ventricular diverticulum or left-dominant arrhythmogenic cardiomyopathy?

Zhang X et al. Left-dominant arrhythmogenic cardiomyopathy

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Abstract

BACKGROUND
Left-dominant arrhythmogenic cardiomyopathy (LDAC) is a relatively rare disease characterized by poor prognosis that exacerbates incidence of sudden cardiac death and ventricular arrhythmias. Clinically, LDAC is constantly overlooked or misdiagnosed as myocardial infarction, myocarditis, and dilated cardiomyopathy, owing to atypical and nonspecific clinical manifestations at an early stage.

CASE SUMMARY
A 57-year-old woman was diagnosed with sinus bradycardia and chronic bifascicular block during a health check. She occasionally experienced mild chest pain and paroxysmal palpitation during activity, in the past two years. Comprehensive auxiliary examinations, including electrocardiogram, echocardiography, coronary computerized tomography angiography, and magnetic resonance imaging, revealed that she had LDAC instead of congenital ventricular diverticulum. The physicians prescribed standard oral therapy for heart failure and implantable cardioverter-defibrillator. Consequently, her left ventricular systolic function and symptoms remained stable at 2-year follow-up after discharge.
CONCLUSION

Based on this case, clinicians need to be aware of LDAC in patients with localized left ventricular lesions and multiple electrocardiographic abnormalities. Multimodality cardiovascular imaging is effective in identification of multiple types of cardiomyopathy and cardiac inner structures.

**Key Words:** Congenital ventricular diverticulum; Left-dominant arrhythmogenic cardiomyopathy; Magnetic resonance imaging; Case report

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**Core Tip:** Left-dominant arrhythmogenic cardiomyopathy is a relatively rare disease, characterized by poor prognosis. We present a case with a dilated left ventricle, that manifested with reduced ejection fraction, multiple outpouchings, left chest leads low voltage, and fragmented QRS. Multimodality cardiovascular imaging diagnosed the patient with left-dominant arrhythmogenic cardiomyopathy instead of congenital ventricular diverticulum. This case alerts that clinicians need to be aware of left-dominant arrhythmogenic cardiomyopathy in patients with localized left ventricular lesions and multiple electrocardiographic abnormalities.

INTRODUCTION

Left-dominant arrhythmogenic cardiomyopathy (LDAC) is a non-hypertrophic, non-hypertensive, and non-valvular progressive cardiomyopathy with fibrofatty myocardium infiltration that prominently occurs in left ventricle[^1]. LDAC might present with ventricular outpouching, which makes it difficult to identify with congenital ventricular diverticulum from the echocardiography[^2]. Here, we present a
case of LDAC with left chest leads low voltage, fragmented QRS (f-QRS), left ventricle (LV) dilation, LV systolic impairment, LV outpouchings, and late gadolinium enhancement of LV myocardium, which was finally diagnosed using multimodality cardiovascular imaging.

CASE PRESENTATION

Chief complaints
A 57-year-old woman, presenting with a dilated left ventricle, reduced ejection fraction, and chronic bifascicular block, was referred to the cardiology department, West China Hospital, on December 10, 2019.

History of present illness
She occasionally experienced mild chest pain and paroxysmal palpitation during activity in the past two years. Her exercise capacity was also mildly reduced. She did not manifest symptoms of fatigue, dizziness, syncope, peripheral edema, and abdominal distention.

History of past illness
The patient had neither prior medical comorbidities nor addictions.

Personal and family history
Her father had a premature sudden cardiac death at the age of 40.

Physical examination
The patient showed good nutrition, active position, clear mind, fluent language, and was cooperative in examination. Examinations on her whole skin and mucous membrane revealed no yellow staining, cyanosis, and bleeding spots. She had a blood pressure and resting heart rate of 120/68 mmHg and 60 beats per min, respectively, and auscultation of both lungs was normal with neither dry nor wet rales. The apical pulse
was located 0.5 cm lateral to the midclavicular line on the left side of the fifth rib, while her heart rhythm was regular. The first and second heart sounds were basically normal, without extra and splitting of the heart sound. No valvular murmurs were detected in any of the auscultation areas. In addition, she did not exhibit any physical signs of heart failure, including edema, ascites, jugular venous distention, and hepatojugular reflux.

**Laboratory examinations**

Results from routine blood test and plasma biochemical examinations, including kidney and liver function, glucose, lipid, and electrolyte, were normal. Similarly, thyroid function, kappa and lambda urine free light chains, as well as coagulation profile, and autoimmune antibodies were also within the normal range. The plasma N-terminal fragment of the pro-brain natriuretic peptide (NT-pro-BNP) was 325 ng/L.

**Imaging examinations**

The electrocardiogram (Figure 1) revealed left anterior branch block, complete right bundle branch block (RBBB), high sidewall abnormal Q wave, and left chest leads (V4-V6) low voltage with poor R wave progression. On the other hand, Holter monitoring (Figures 2 and 3) revealed sinus arrest with a 1.74 s R-R interval, multisource premature ventricular beats, non-sustained ventricular tachycardia with an RBBB pattern, and f-QRS in leads V3-V6. Transthoracic echocardiography (TTE) showed a dilated left ventricle (LV) with a diameter of 60 mm, as well as a reduced LV ejection fraction (EF) of 35%, and a left ventricular apex cystic outpouching (12 mm × 13 mm) that displayed synchronous contractility (Figure 4, Panel A, B and C). Myocardial contrast echocardiography (MCE) revealed contractile outpouching without obvious filling defects (Figure 4, Panel D). Coronary computerized tomography angiography (CCTA) revealed right dominant coronary artery circulation without obvious stenosis, LV multiple outpouchings, uneven thickness of the LV wall (Figure 5, Panel A, B, E and F), hypodense region (CT value -90~-114 HU) at localized myocardium of LV septum (Figure 5, Panel C) and free wall (Figure 5, Panel D). These findings were consistent
with profiles of fatty tissue infiltration. In addition, we used cardiac magnetic resonance imaging (CMRI) to evaluate the cardiac structure, bilateral ventricular function, segmental movement, and tissue characterization in the patient. CMRI results revealed LV dilatation, abnormal activity of the LV wall (Figure 6, Panel A and B), an outpouching at the LV apex, a low signal in the septum myocardium midwall after contrast injection (Figure 6, Panel C). Moreover, late gadolinium enhancement (LGE) in the midwall of the left ventricular septum and free wall myocardium were also evident (Figure 6, Panel D).

**Genetic testing**
High-throughput sequencing revealed no genetic variation with high clinical phenotype correlation and sufficient evidence of pathogenicity.

**FINAL DIAGNOSIS**
These findings highly pointed to LDAC.

**TREATMENT**
After comprehensive evaluation of the patient, we prescribed sacubitril valsartan sodium tablets (50 mg bid) and spironolactone (20 mg qd). We did not administer beta-blocker in this case, owing to multiple atrioventricular conduction abnormalities. In addition, she was given low-dose thiazide diuretics when needed to relieve edema and congestion symptoms. Three months later, her left ventricular size and systolic function had not changed compared to baseline. Consequently, she was subjected to an implantable cardioverter-defibrillator (ICD) after full discussion in our department.

**OUTCOME AND FOLLOW-UP**
Two years later, we re-evaluated her symptoms and clinical indexes, and found that the symptoms improved after taking standard oral medication for ejection fraction reduced heart failure. The pacemaker program did not record sustained ventricular tachycardia
or ventricular fibrillation. Echocardiography revealed that left ventricular size and systolic function were almost similar to two years prior to treatment.

**DISCUSSION**

This case affirms the need for clinicians to be aware of LDAC in patients with localized left ventricular lesions and multiple electrocardiographic abnormalities. Notably, multimodality cardiovascular imaging and electrocardiogram (ECG) should be considered in this situation.

The patient in the present case revealed various ECG abnormalities, including sinus node dysfunction, chronic bifascicular block, abnormal Q wave, left chest leads low voltage (V4-6), poor R wave progression in leads V4-V6, and f-QRS in leads V3-V6. These were all indicative of left ventricular myocardial abnormality and extensive conduction system disorder. f-QRS, which has been defined as the presence of additional R’ waves or a notch in the R or S wave in two contiguous leads, indicates myocardial scarring and represents distortion of signal conduction as well as depolarization processes within ventricles. Previous studies have shown that f-QRS is an independent predictor for cardiac events, ventricular arrhythmias, and sudden cardiac death. Notably, it has been detected in patients with various structural heart or primary electrical diseases, such as Brugada syndrome, arrhythmogenic right ventricular dysplasia, and acquired long QT syndrome. Therefore, careful differential diagnosis for cardiomyopathy was imperative for the patient in the present case. Furthermore, there is need to consider multimodality cardiovascular imaging.

CMRI combined with CCTA is effective in identification of multiple types of cardiomyopathy and cardiac inner structures. Initially, we considered the left ventricular apex outpouching with a thick wall, narrow communication, and synchronous contractility to be a diverticulum, based on evidence from echocardiography and MCE. However, CCTA and CMRI generated more details for differential diagnosis. Previous studies have shown that CCTA, a noninvasive approach, can effectively distinguish outpouchings caused by myocardial infarction.
and ischemic cardiomyopathy related to occlusion (or lack thereof) of the coronary arteries\textsuperscript{[7,8]}. Furthermore, CMRI has a unique advantage in identifying cardiomyopathy. Black blood with T1 and T2 sequences as well as dynamic bring blood were used to evaluate the cardiac structure, tissue characterization, bilateral ventricular function, and segmental movement. In addition, delayed enhancement imaging following administration of gadolinium can result in more information on fibrosis, scarring, and fat infiltration in the local myocardium\textsuperscript{[9]}. In the present case, CCTA and CMRI results revealed LV septum and free wall local myocardium replaced by fatty tissue, as well as LV midwall LGE, multiple LV outpouchings, uneven thickness of the LV wall, without stenosis of coronary arteries. These abnormalities were accompanied by non-sustained ventricular tachycardia with an RBBB pattern and f-QRS in the left chest leads. Consequently, we considered that this patient had arrhythmogenic cardiomyopathy (ACM).

ACM refers to a category of non-hypertrophic, non-hypertensive, and non-valvular progressive cardiomyopathy with fibrofatty myocardium infiltration\textsuperscript{[10]}. Previous studies have classified ACM into classical arrhythmogenic right ventricular cardiomyopathy (ARVC), LDAC, and biventricular involvement categories\textsuperscript{[11]}. The patient in the present study was eventually diagnosed with LDAC. LDAC, which was first described by Sen-Chowdhry et al\textsuperscript{[1]} in 2008, has been easily overlooked or misdiagnosed as myocardial infarction, myocarditis, and dilated cardiomyopathy in clinical practice. Notably, LDAC is a relatively rare disease. For example, it accounted for less than 0.15\% of 35845 consecutive patients who were referred for CMR examinations in Fuwai Hospital (Beijing, China), National Center for Cardiovascular Diseases\textsuperscript{[12]}. Clinically, LDAC patients mainly manifest palpitations, presyncope, exertional dyspnea, and chest pain with normal coronary angiography, with only a handful of cases found to be asymptomatic\textsuperscript{[12,13]}. Patients with LDAC have poor prognosis. For example, Feliu et al\textsuperscript{[12]} found that 32.4\% of all LDAC patients studied manifested major adverse cardiovascular events, which were mainly accompanied by sudden cardiac death and ventricular arrhythmias, during a mean follow-up of 3.74
years. At present, no specific diagnostic criteria exist for LDAC. In 2008, Dr. Chowdhry established the following initial diagnostic features of LDAC: 1. Arrhythmia: sustained or non-sustained ventricular tachycardia; 2. Imaging: (1) LV aneurysms, (2) mild LV dilation and/or systolic impairment; 3. Biopsy/CMRI: (1) cardiomyocyte loss with fibrofatty replacement on histology, (2) extensive LGE of LV myocardium (with subepicardial/midmyocardial distribution); 4. Unexplained T-wave inversion in V5, V6 ± V4, I, and AVL. Recently, Corrado and his colleagues suggested that the following elements should be considered as LDAC: (1) ECG changes, such as low QRS voltages in limb leads and inverted T waves in the inferolateral leads; (2) ventricular arrhythmias with a RBBB pattern; and (3) structural and functional imaging features consistent with ‘hypokinetic and fibrotic LV’. Interestingly, the ultrasonologist initially misdiagnosed the patient in the present study as congenital ventricular diverticulum (CVD), according to the left ventricular apex cystic outpouching displayed synchronous contractility with the corresponding cardiac chamber.

CVD, first described in 1816, was often asymptomatic and incidentally detected during a regular physical check-up. Generally, the left ventricular diverticulum was in a thick wall, comprising endocardium, myocardium, and pericardium, with a narrow communication between the cavity and ventricular, and displayed synchronous contractility with the LV. This was likened to an appendix originating from the ventricle. The left ventricular diverticulum has an average size that varies from 0.5 cm to as large as 8-9 cm. Notably, the left ventricular diverticulum not only has low prevalence, as evidenced by 0.4%-2.2% across different studies, but has also been associated with occurrence of other congenital abnormalities, including septal defects, dextrocardia, and pulmonary stenosis. Generally, CVD combined with midline thoraco-abdominal congenital abnormalities, diaphragmatic and sternal defects, and partial absence of diaphragmatic pericardium is referred to as the Cantrell’s syndrome. CVD has the atypical and nonspecific clinical manifestations at an early stage, namely arrhythmias, cardiac rupture, heart failure, and embolism, which make it easily confused with LDAC. However, some of these features can be adopted during the
differential diagnosis between CVD and LDAC. Firstly, most CVD are single and located at the cardiac apex\textsuperscript{[20,21]}. Secondly, the left ventricular wall exhibits neither signal alterations nor signs of necrosis or fibrous tissue in CVD cases\textsuperscript{[22]}. Thirdly, CVD patients exhibit more frequent extracardiac anomalies than those with LDAC\textsuperscript{[19]}. Fourthly, the size of CVD does not change over the time, suggesting a benign course\textsuperscript{[23]}. However, the patient in the present study not only manifested multiple left ventricular outpouchings but also exhibited uneven-thickness left ventricular wall with multiple flaky fatty infiltrations. This interesting case indicates that clinicians should not ignore LDAC upon detecting left ventricle outpouching in TTE.

Although myocardial biopsy is the gold standard diagnostic criterion, this patient refused this invasive examination. After comprehensively analyzing a combination of the medical history and positive clues on auxiliary examinations, including ECG, TTE, CCTA, and CMRI, the specialists in our department unanimously diagnosed the patient with LDAC. She was subsequently administered with standard oral therapy for heart failure with reduced ejection fraction and ICD. The patient was very satisfied with the process of diagnosis, treatment, and follow-up.

CONCLUSION
LDAC is a relatively rare disease, which requires multimodality cardiovascular imaging for diagnosis. CMR combined with CCTA is an excellent approach for identification of multiple types of cardiomyopathy and cardiac inner structures. From the present case, clinicians are advised to consider LDAC in patients with localized left ventricular lesions and multiple electrocardiographic abnormalities.

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