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Case Report

Young patient presenting with cardiogenic shock and refractory ventricular tachycardia: a case of unsuspected arrhythmogenic cardiomyopathy leading to urgent heart transplantation

Benoit Yu[1], Nickolas Poulakos[1], Alexander Beaulieu-Shearer[2], Pierre Yves Turgeon[3], Sylvain Trahan[4], David Belzile[3], Mario Sénéchal[3]

[1]Faculty of Medicine, Université Laval, Québec, QC, Canada; [2]Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada; [3]Department of Cardiology, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada; [4]Department of Pathology, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada

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Abstract: Arrhythmogenic right ventricular cardiomyopathy is an important differential diagnosis in young patients presenting with palpitations and/or dyspnea and must be appropriately investigated. A 23-year-old man presented with cardiogenic shock and monomorphic ventricular tachycardia. He reported palpitations and progressive dyspnea for more than two years, but those symptoms were attributed to anxiety without any further investigation by his family physician. Investigations after the catastrophic presentation in our center suggested terminal right-sided heart failure with severe hepatic insufficiency and acute kidney injury. The patient benefited from extracorporeal membrane oxygenation, followed by an urgent heart transplant 16 days later after the exclusion of liver cirrhosis. Histopathologic analysis of the explanted heart confirmed arrhythmogenic cardiomyopathy.

Keywords: Arrhythmogenic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, heart transplantation, echocardiography

Introduction

Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiomyopathy caused by desmosomal and non-desmosomal protein mutations [1]. Up to 16 genes encoding proteins have been linked with ACM [1]. The sensitivity of genetic testing remains, however, low at 55% for pathogenic mutations in ACM [1]. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is the isolated RV form of ACM. Nevertheless, it is now well known that LV may be involved in up to 50% of the cases [1]. The predominant mode of presentation of patients with ARVC are palpitations, syncope, or sudden death [2]. Various phenotypes are now described, but the disease classically presents with ventricular arrhythmias and progressive right-sided heart failure.

Although endomyocardial biopsy or autopsy remain valuable tools to confirm the diagnosis of ARVC, there is no single gold standard due to its variable phenotype, unlike most other types of cardiomyopathies [3]. Currently, ACM diagnosis mainly relies on the 2020 International criteria [3, 4]. These criteria include imaging, pathology, electrophysiologic findings (repolarization, repolarization, conduction, and arrhythmic abnormalities), and family history/genetics. The diagnosis is defined as definite (two major or one major + two minor or four minor), borderline (one major + two minor or three minor), or possible (two minor) according to the number of criteria met. The disease is subsequently categorized as ARVC (isolated RV involvement), arrhythmogenic left ventricular cardiomyopathy (ALVC), or biventricular (ARVC + ALVC). Of note, pathogenic or likely pathogenic

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ACM-causing gene mutation is required to confirm ALVC diagnosis.

Imaging features (2D echocardiogram, cardiac magnetic resonance, or angiography) of ARVC include regional wall motion abnormalities of the RV, RV dilation, and RV systolic dysfunction [3]. More precisely, the 2020 International major criteria for ARVC by echocardiography are defined as regional RV akinesia, dyskinesia, or bulging and one of the following: global RV dilatation (an increase of RV end-diastolic volume according to the imaging test-specific nomograms for age, sex, and body surface area) or global RV systolic dysfunction (reduction of RV ejection fraction according to the imaging test-specific nomograms for age and sex) [1, 3]. On electrocardiogram, epsilon waves on the right precordial leads (V1 to V3) represent a minor criterion for ARVC diagnosis by the 2020 International criteria. This depolarization abnormality was previously a major criterion, but it is an infrequent finding in ARVC patients, identified in approximately 10-33% of ARVC patients [1].

The pathologic findings on endomyocardial biopsy or autopsy are the fibrous replacement of the myocardium in ≥1 sample, with or without fatty replacement of tissue [1, 3]. Yet, the usefulness of endomyocardial biopsy in the ARVC workup remains controversial due to its limited sensitivity, estimated at around 50% [5]. However, electroanatomic voltage mapping-guided EMB may be key to increasing the sensitivity of biopsies for ARVC [5].

Many patients with ARVC will remain asymptomatic for decades before developing symptoms [6]. The typical clinical features include shortness of breath, palpitation, dizziness/syncope, and signs of right-sided heart failure [6]. Unfortunately, a few patients will suffer from sudden cardiac death [7]. ARVC generally presents in adulthood, during the third and fifth decades of life [8]. However, this disease can also be diagnosed during the second decade. After the disease is detected, the transplantation-free survival is between 5-10% five years after the initial presentation [8, 9]. Currently, treatment options are limited to guideline-directed medical therapy in patients with heart failure and beta-blocker, antiarrhythmic drugs (amiodarone, sotalol, and flecainide), and implantable cardioverter-defibrillators for arrhythmia management and prevention. In patients with ARVC and recurrent sustained monomorphic VT who have failed or are intolerant to medical management, catheter ablation can also be considered for reducing recurrent VT and ICD shocks. Heart transplantation is the ultimate option in patients with refractory HF and arrhythmia.

ARVC is an important differential diagnosis in young patients presenting with palpitations and/or dyspnea and must be appropriately investigated. The non-recognition of this pathology can have catastrophic consequences, as evidenced by the following case.

Case report

A 23-year-old man presented to the emergency room with acute onset nausea and vomiting associated with fatigue, dizziness, and palpitations over the last 48 hours. He had no significant medical or family history of cardiomyopathy or sudden cardiac death. However, the patient reported palpitations and progressive dyspnea on exertion for over two years. The patient sought medical attention, but his symptoms were wrongfully attributed to anxiety by his family physician. No further investigations were initially conducted despite being indicated.

On arrival in the emergency room, the patient was tachycardic (179 bpm), hypotensive (85/50 mmHg), and tachypneic (24 respirations per minute). The initial electrocardiogram showed monomorphic ventricular tachycardia (VT) with left bundle branch block morphology, precordial transition in lead V4, and inferior axis (**Figure 1A** and **1B**). A transthoracic echocardiographic study showed a significantly dilated right ventricle (RV) with a severely reduced RV systolic function (parasternal long-axis RV outflow tract 63 mm, parasternal short-axis RV outflow tract 60 mm), with torrential tricuspid regurgitation, and globally preserved left ventricular ejection fraction (**Figure 2** and Videos S1-S4). The clinical evaluation suggested severe right ventricular (RV) dysfunction associated with probable secondary hepatic insufficiency and acute kidney injury (patient's laboratory values at initial presentation are listed in **Table 1**). Cardioversion of the VT to sinus rhythm was successfully performed. Following the VT termination, the electrocardiogram showed

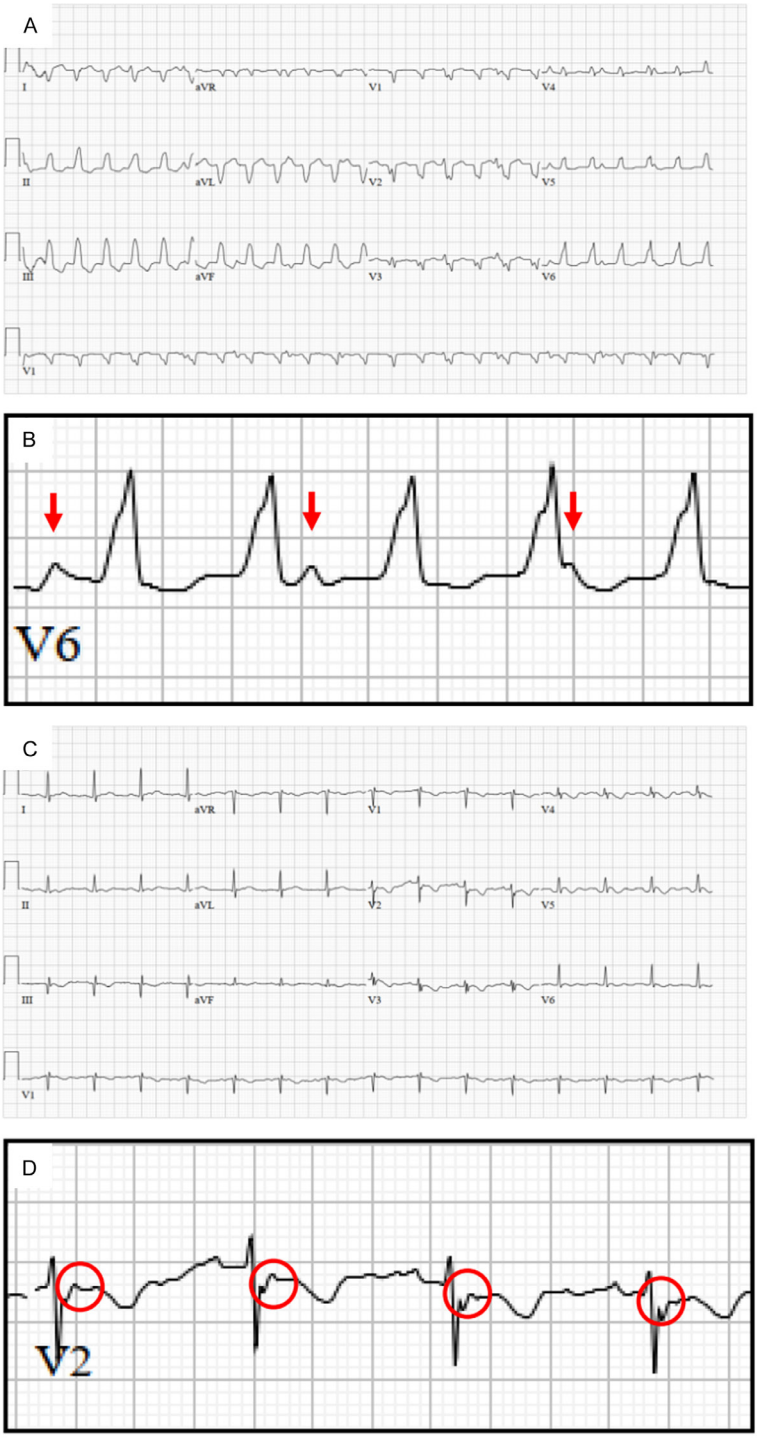

Figure 1. Electrocardiographic findings at initial presentation and post-ventricular tachycardia termination. (A) Electrocardiogram at baseline demonstrating monomorphic ventricular tachycardia with left bundle branch block morphology and precordial transition in lead V4 and inferior axis. (B) Atrioventricular dissociation is also seen. (C) Electrocardiogram, post ventricular tachycardia termination, demonstrating sinus rhythm with inverted T waves in leads V1 to V3, epsilon waves in V2 to V5 (D).

inverted T waves in the right precordial leads and epsilon waves in V2 to V5 (**Figure 1C** and **1D**). The persistent profound shock associated with significant end-organ injuries led to the initiation of venoarterial extracorporeal membrane oxygenation (VA-ECMO) support. Renal replacement therapy was also initiated for RV preload optimization in the setting of cardiogenic shock and concomitant acute kidney injury. Further investigations to assess the liver included an abdominal ultrasound that showed uniform liver parenchyma and an abdominal computed tomography that revealed moderate ascites in the paracolic gutter and Douglas's pouch, which indicated a subacute or chronic disease. To definitively exclude cardiac cirrhosis, the patient underwent a liver biopsy that demonstrated congestive hepatopathy without fibrosis. Hepatic congestion and renal perfusion improved with VA-ECMO and medical treatment. However, VA-ECMO weaning was deemed impossible because of end-stage RV failure, and the patient subsequently underwent urgent heart transplantation 16 days after presentation. The postoperative evolution was favorable, with rapid weaning of inotropic support, normalization of end-organ parameters, and transfer to the cardiac surgery ward within a few days. No significant liver dysfunction was noted post-transplant, with preserved synthetic function and normalization of liver enzymes. Standard immunosuppressive therapy (tacrolimus, mycophenolic acid and prednisone) was introduced, and the patient was discharged home a month later following adequate teaching and rehabilitation. A macroscopic examination of the explanted heart showed severe RV dilation (**Figure 3A** and **3B**).

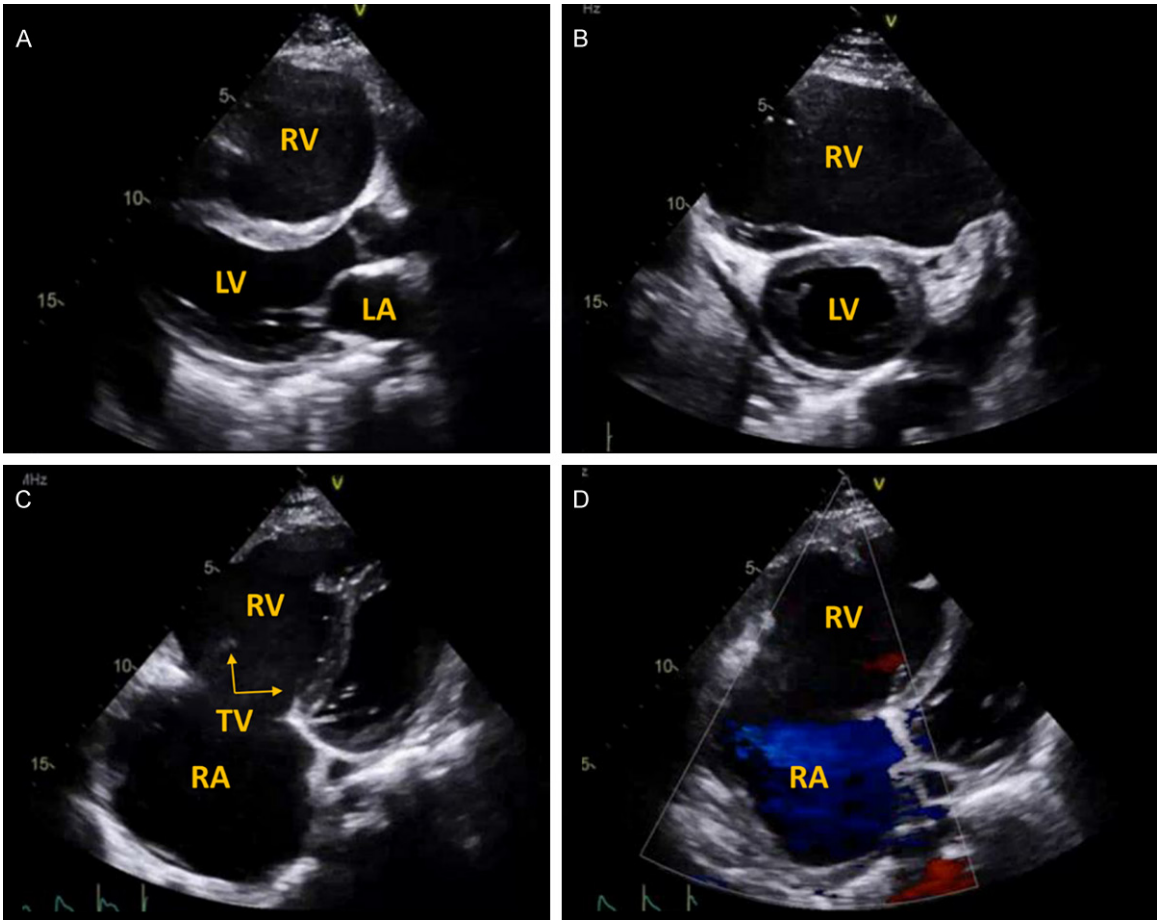

Figure 2. Baseline transthoracic echocardiogram. A. Parasternal long axis view demonstrating an extremely dilated right ventricle. Deviated septum in systole-diastole, indicating significant pressure overload. B. Parasternal short axis view demonstrating severe right ventricle enlargement with severe systolic dysfunction and a preserved left ventricular size and systolic function. C. The apical right ventricle-focused view demonstrates the absence of coaptation of the tricuspid leaflet with severe tenting. D. The color Doppler image confirms laminar regurgitant flow associated with very wide regurgitant orifice and torrential tricuspid regurgitation. Abbreviations: LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle, TV: tricuspid valve.

Histopathologic analysis of the heart demonstrated an RV with a fine discontinuous layer of cardiomyocytes with fibrofatty replacement of the wall compatible with arrhythmogenic cardiomyopathy (**Figure 3C**). There was mild involvement of the epicardial aspect of the left ventricle (LV), which showed focal fibrofatty replacement with a thickness of 3 mm. The patient underwent genetic testing, but no causative mutation was found despite whole-exome sequencing. The patient was followed at our heart transplant clinic for the past five years without significant complications post-transplantation. The follow-up also included frequent transthoracic echocardiograms, routine laboratory tests and clinical follow-up visits confirming the absence of significant complications post-transplantation, with preserved graft function.

Discussion

This case highlights the potential implications of delayed diagnosis of ARVC patients. Although the overall prognosis of this disease is relatively good, underrecognition can lead to catastrophic presentation requiring advanced therapies.

ACM may go underdiagnosed for numerous years or decades before being diagnosed, leading to potentially life-threatening complications, such as ventricular arrhythmia and cardiogenic shock. ACM accounts for up to 20% of arrhyth-

Table 1. Patient laboratory values at the time of presentation in the emergency department

Laboratory Test	Patient value (normal value)
ALT (U/L)	1589 (<60)
AST (U/L)	868 (<45)
LDH (U/L)	3679 (0-225)
Total bilirubin (μmol/L)	51 (0-17)
Direct bilirubin (μmol/L)	20 (<4)
ALP (U/L)	74 (40-120)
Albumin (g/L)	38 (35-50)
INR	13 (<1.2)
Urea (mmol/L)	24 (1.7-8.5)
Creatinine (μmol/L)	137 (50-110)

Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, INR: international normalized ratio, LDH: lactate dehydrogenase.

mogenic death cases in young patients [7]. Early detection of the disease in these patients may help reduce the ARVC sudden cardiac death burden with early ICD implantation as recommended by the 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy [10].

The absence of a gold standard complicates the diagnosis of ARVC. A high degree of suspicion and extensive testing is needed to improve sensitivity for ARVC. A previous study showed that imaging (echocardiography and cardiac magnetic resonance imaging) contributes to the "definite" diagnosis of ACM with a sensitivity of only 46% and 33%, respectively, highlighting the importance of combining imaging, 12-lead electrocardiogram, and genetic testing in young patients with suspected ACM [2]. In our case, the diagnosis of ARVC could only be confirmed after transplantation with the histopathologic analysis of the explanted heart. Early referral to a cardiogenetic team is key to improving diagnostic accuracy.

ARVC remains a rare cause of heart transplantation. In a study listing more than 35,000 heart transplants identified from the United Organ Sharing Thoracic Registry between 1994 and 2011, only 73 patients had ARVC (0.2%) [11]. Of this number, 11% were under 18 years old. Although ACM represents a small proportion of transplanted patients, this intervention is not uncommon in all ACM patients. In a large cohort of ACM patients who underwent heart transplantation and their non-transplanted ACM probands, 17% of the cohort belonged to the former group. Advanced heart failure was the indication for transplantation for most patients (90%). Moreover, that study also suggested an association between a young age of onset of ACM and the need for heart transplantation, similar to our case [12]. ARVC patients requiring transplantation must be thoroughly investigated to rule out any contraindication for heart transplantation prior to listing, as long-standing undiagnosed RV dysfunction may be associated with chronic venous congestion causing congestive hepatopathy and potentially liver cirrhosis and also chronic kidney disease due to cardiorenal syndrome. In our case, a liver biopsy was required to rule out liver cirrhosis. A previous study demonstrated that imaging alone had limited sensitivity for liver cirrhosis in pretransplant assessment [13].

The use of ECMO in ARVC cases appears far less common but has been previously described in the literature. Moreover, ECMO has also been used as a bridging strategy in VT storms. In patients presenting with cardiogenic shock, predominantly triggered by RV failure, inotropes are usually the first-line therapy, but mechanical support may be required. ECMO is more widely available, but in patients with isolated RV dysfunction, isolated RV support with Impella RP® or Protek Duo® may be a better option. Temporary mechanical support with a surgically implanted right-sided CentriMag® is also another option. However, physicians should be aware that fully supporting a failing RV may uncover previously undiagnosed LV dysfunction with the retrieved LV preload and associated hemodynamic changes.

Conclusions

Even if most cases of ACM manifest between the third and fifth decades of life [8], in young patients presenting with palpitations and/or dyspnea, appropriate cardiac investigations (electrocardiogram and transthoracic echocardiogram) should be conducted to exclude important diagnoses like ACM, where delayed recognition may result in catastrophic heart failure, ventricular arrhythmias, and sudden cardiac death.

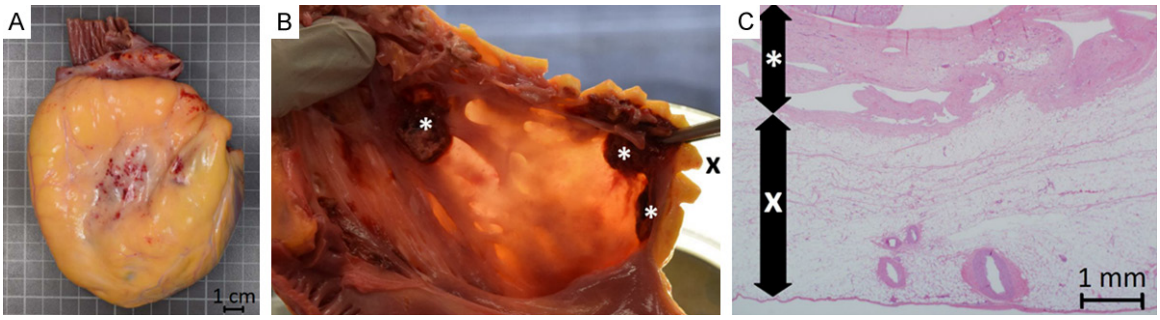

Figure 3. Pathologic examination of the explanted heart. Macroscopic and microscopic explanted heart examination. A. Explanted heart, gross examination, anterior view. Severe and diffuse yellowish fatty and fibrous infiltration of the right ventricle. B. Explanted heart, gross examination, right ventricle luminal view. Severe and diffuse yellowish fatty and fibrous infiltration of the right ventricle seen by trans-illumination with a light source (x) with multiple mural thrombi (*). C. Explanted heart, right ventricle microscopic examination (hematoxylin and eosin stain; magnification 2× - scale bar 1,000 µm = 1 mm). Transmural fibrous (*) and fat (x) right ventricle.

Disclosure of conflict of interest

None.

Abbreviations

ACM, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; ECMO, venoarterial extracorporeal membrane oxygenation; LV, left ventricle; RV, right ventricle.

Address correspondence to: Dr. Mario Sénéchal, Department of Cardiology, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725, Chemin Sainte-Foy, Québec, QC G1V 4G5, Canada. E-mail: mario.senechal@criucpq.ulaval.ca

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