Late evolution of arrhythmogenic cardiomyopathy in patients with initial presentation as idiopathic ventricular fibrillation

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Introduction

Arrhythmogenic cardiomyopathy (ACM), also known as arrhythmogenic right ventricular dysplasia/cardiomyopathy, is an inheritable heart muscle disorder in which sudden cardiac death due to ventricular fibrillation (VF) may occur unexpectedly as the first manifestation of the disease.[1] This event is usually preceded by a long preclinical phase.[2]

Thus, prior to this event, the disease may frequently go unnoticed owing to the absence of relevant symptoms. This early presymptomatic stage has been defined as "concealed stage," which does not necessarily mean absence of disease; in the absence of symptoms, criteria for ACM diagnosis may even be already present.[2] Since 2010, ACM diagnosis is made according to revised Task Force Criteria (2010 TFC) obtained by international consensus.[3] Fulfillment of these 2010 TFC (ie, presence of 2 major, 1 major plus 2 minor, or 4 minor criteria) is required for "definite" ACM diagnosis. Although fulfillment of TFC is required for definite ACM diagnosis, in the early disease stage it is conceivable that VF may occur in the presence of most but not all criteria. These cases are often regarded as idiopathic VF (IVF).

In contrast to VF due to ACM, in IVF all known cardiac, respiratory, metabolic, and toxicologic etiologies should have been excluded by the clinical evaluation available at the time of the arrhythmic event.[4] However, in our experience, some survivors of initially unexplained cardiac arrest may develop "definite" ACM years after the index event,[5] either by progression of the disease or by improvement of diagnostic tools.

KEYWORDS Arrhythmogenic cardiomyopathy; Diagnostic testing; Disease progression; Electrophysiology; Idiopathic ventricular fibrillation; Ventricular arrhythmia

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KEY TEACHING POINTS

- Idiopathic ventricular fibrillation is a diagnosis by exclusion. Absence of diagnosis does not mean absence of disease.
- Reevaluation of diagnosis during follow-up is important, as diagnosis of genetic disease can impact treatment and familial risk stratification.
- Diagnosis of arrhythmogenic cardiomyopathy in a later stage in patients initially presented with idiopathic ventricular fibrillation may be due to improvement of diagnostic tools, progression of disease, or misinterpretation of initially available data.

We present 2 cases of ACM patients with no or minimal disease at the time of their initial cardiac arrest episode. These episodes occurred in 1991 and 1995, thus before availability of the 2010 TFC. This means that ACM diagnosis was initially based on the less sensitive TFC published in 1994[6] in 1 case, and on clinical and electrocardiogram (ECG) characteristics in the other.

Case reports

Case 1

A 24-year-old man collapsed twice in 1 year while playing in a soccer match. The first time, in 1991, he regained consciousness shortly after the start of resuscitation. Clinical evaluation was inconclusive. The second time, in 1992, he received 2 external defibrillator shocks because of VF. Resuscitation was successful and he was admitted for diagnostic evaluation. ECG showed sinus rhythm with intraventricular conduction delay, including prolonged terminal activation duration (70 ms), and J-point elevation in the inferior leads (Figure 1A). History, Holter monitoring, and exercise test were unremarkable, and no ventricular extrasystoles

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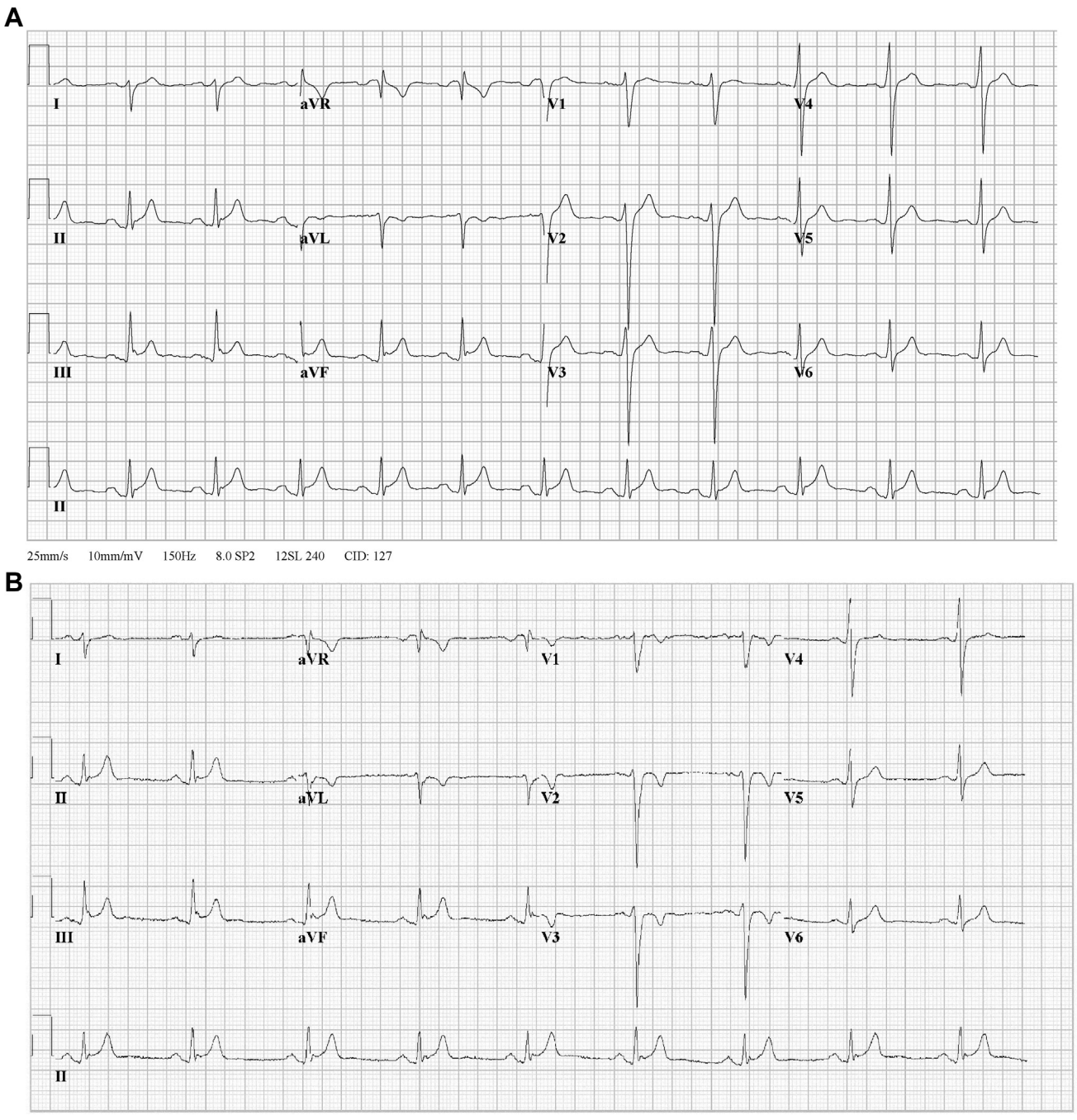

Figure 1 **A:** A 12-lead electrocardiogram (ECG) while off antiarrhythmic drugs, showing sinus rhythm, QRS right axis deviation, QRS width 140 ms, and prolonged terminal activation duration in V_2 (70 ms). Clear J-point and ST elevation in II, III, and aVF. **B:** ECG after 10 years of follow-up, showing negative T-waves in V_1–V_3.

were reported. Family history was negative for sudden cardiac death. Echocardiogram showed normal cardiac function and biventricular dimensions; however, a local abnormality under the tricuspid valve was noted. Transesophageal echocardiogram was performed, in which this abnormality was characterized as prolapse of a tricuspid valve leaflet. During electrophysiologic study, a prolonged HV interval of 60–70 ms was measured. Right ventricular (RV) stimulation induced polymorphic ventricular tachycardia (VT) starting as monomorphic VT with left bundle branch block morphology and superior axis. Other diagnostic tests, including coronary angiogram, myocardial biopsy, and ergonovine provocation test, were normal. An implantable cardioverter-defibrillator (ICD) was implanted and he was discharged. In the absence of an obvious etiology, IVF was the initial diagnosis. Cardiac magnetic resonance imaging (CMR) and signal-averaged ECG were not performed.

Ten years after the initial presentation, negative T waves were recorded in V_1–V_3 (Figure 1B). Thus, he went on to fulfill definite ACM diagnosis criteria.

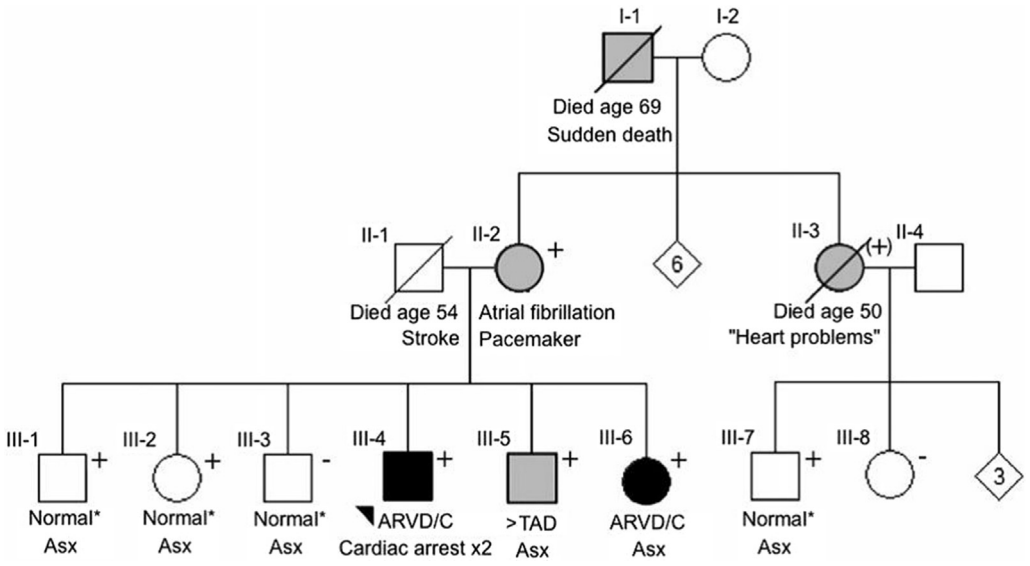

Figure 2 Pedigree of the p.Leu729del mutation carrier (case 1) reveals co-segregation of the variant with the arrhythmogenic cardiomyopathy phenotype with reduced penetrance. ARVD/C = arrhythmogenic right ventricular dysplasia/cardiomyopathy; Asx = asymptomatic; >TAD = prolonged terminal activation duration. Symbols: square = male; circle = female; + = *SCN5A* mutation carrier; (+) = obligate *SCN5A* mutation carrier; solid = clinical ARVD/C diagnosis; gray = clinical symptoms and/or borderline ARVD/C diagnosis; empty = negative phenotype for ARVD/C. *No abnormalities on comprehensive cardiac evaluation including 12-lead electrocardiogram, Holter monitoring, and cardiac imaging. (From Te Riele and colleagues.[14])

On follow-up echocardiogram, there were no signs of tricuspid valve prolapse anymore, but careful reevaluation of imaging showed subtricuspid dyskinesia. After 16 years, RV dilatation was noted (echocardiogram 2008: dilated, hypokinetic RV; parasternal long-axis RV outflow tract [RVOT]: 32 mm, parasternal short-axis RVOT: 35 mm). Consecutive molecular genetic testing revealed an unclassified variant in the *DSG2* gene and a p.Leu729del mutation in the sodium channel gene *SCN5A*. Familial co-segregation supported pathogenicity of this *SCN5A* mutation (Figure 2). During 25 years of follow-up, he remained free of ventricular tachyarrhythmias.

In this case, fulfillment of 2010 TFC in follow-up was owing to disease progression (eg, progression of precordial T-wave inversions), misinterpretation of clinical evaluation (eg, wrong interpretation of subtricuspid dyskinesia as tricuspid valve prolapse), and incomplete clinical evaluation (no CMR was performed).

Case 2

In 1995, a 25-year-old man collapsed during light chores while at work in a café. He was resuscitated and admitted to the intensive care unit. His history was unremarkable and there was no sudden death in his family. Electrocardiography showed sinus rhythm with negative T waves in leads V_4–V_6 and low voltage in extremity leads (Figure 3A). Echocardiogram, coronary angiogram, and myocardial biopsy were normal. The left ventricular ejection fraction was 62% by echocardiography. During electrophysiologic study, RVOT stimulation showed inducibility of a monomorphic VT with left bundle branch block morphology and vertical axis. An ICD was implanted and he was discharged. Thus, at initial evaluation, he fulfilled 2 minor TFC for ACM diagnosis, indicating IVF as initial diagnosis.

During follow-up, he experienced appropriate ICD shocks because of VT episodes. Subsequent Holter monitoring showed 870 premature ventricular complexes in 24 hours. Fourteen years after the event, he showed signs of heart failure with dilated ventricles (Figure 3B, echocardiogram 2009: RVOT/RV lateral wall akinesia, inferior RV dyskinesia, parasternal long-axis RVOT: 56 mm, parasternal short-axis RVOT: 59 mm, and left ventricular ejection fraction 25%). Genetic testing revealed an unclassified variant in the plakophilin-2 gene and a pathogenic c.40-42delAGA mutation in the phospholamban (*PLN*) gene. CMR and signal-averaged ECG were not performed.

Fulfillment of ACM diagnosis criteria during follow-up was owing to disease progression (eg, clinical signs of heart failure and increase in echocardiographic measurements during follow-up) and misinterpretation of clinical evaluation (eg, under-recognition of biventricular/left-dominant disease in ACM at time of first symptoms).

Discussion

Absence of diagnosis does not mean absence of disease

We present 2 cases with an initial presentation of nonfatal cardiac arrest due to underlying VF. Since only nonspecific minor abnormalities were identified at the time of presentation, these cases were diagnosed as IVF. Many years after the initial presentation, TFC fulfillment led to a definite diagnosis of ACM (Table 1).

The presented cases suggest that IVF or "concealed" ACM does not necessarily mean absence of disease, and periodic reevaluation of suspected ACM cases may lead to a definite diagnosis. Diagnosing ACM in former IVF patients is important, as it provides additional management options such as

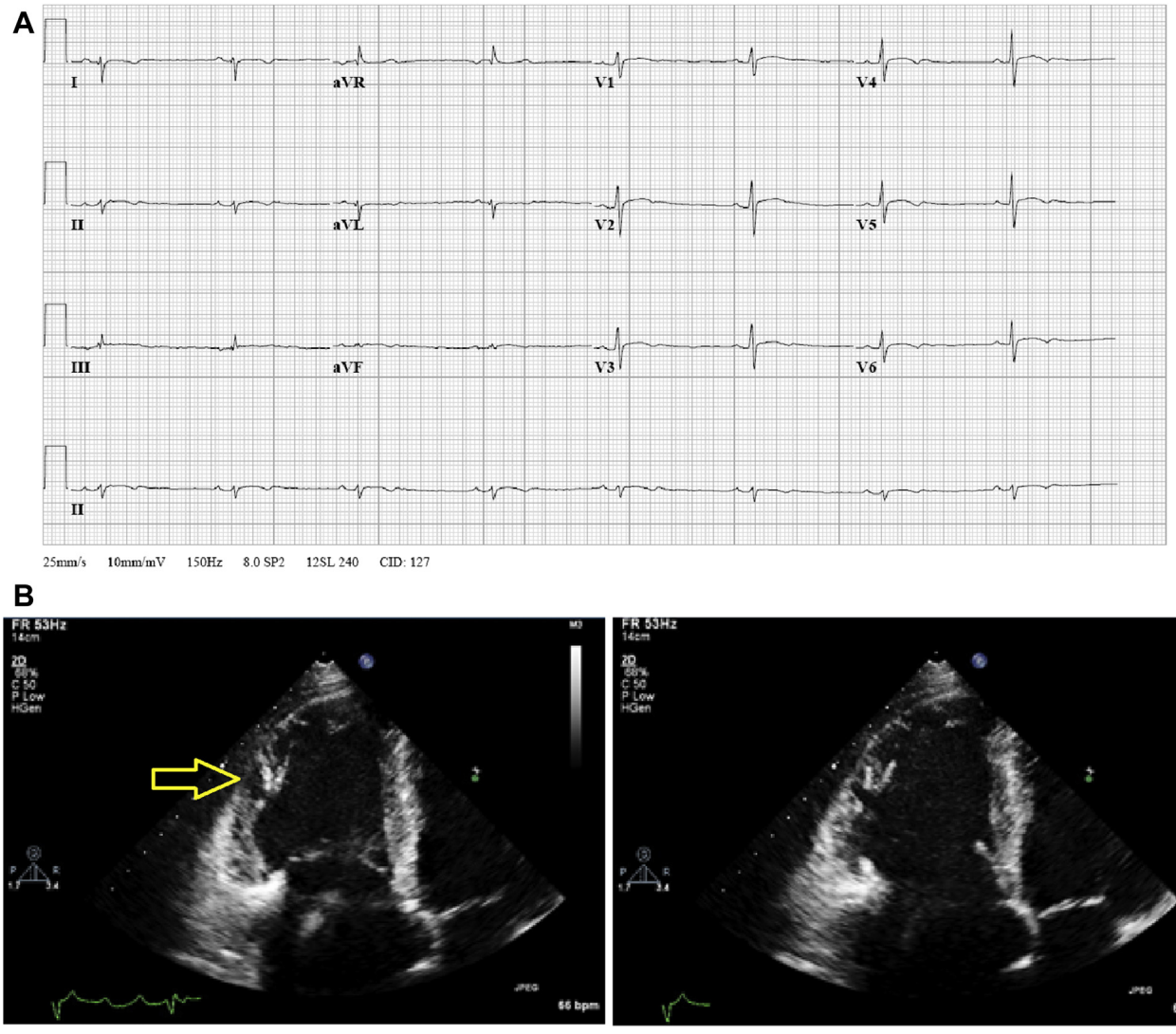

Figure 3 **A:** A 12-lead low-voltage electrocardiogram while off antiarrhythmic drugs showing normal sinus rhythm and QRS right axis deviation. Negative T waves in left precordial recordings and I, II, and aVF. **B:** Transthoracic echocardiogram during follow-up showing a dilated right ventricle with subtricuspid aneurysm (*arrow*).

pharmacologic therapy and lifestyle interventions.[2] More importantly, in family members of patients with a genetic disorder, a correct diagnosis may pave the way for cascade screening as a first step toward arrhythmic risk stratification.

Reevaluation of diagnosis

IVF is a diagnosis by exclusion in which initial evaluation does not identify an underlying cause. Diagnosing a specific disease, such as ACM, during follow-up may be a consequence of (1) improvement in diagnostic tools, (2) disease progression, or (3) misinterpretation of initially available data. These are common challenges in clinical practice, and a combination of these is illustrated in this report; our cases may be part of a larger patient population that is not diagnosed at the time of clinical presentation.

Improvement in diagnostic tools

The ability of diagnostic tests to detect electrical and structural abnormalities in the initial evaluation of patients suspected of ACM varies considerably. Qualitative assessment of RV angiogram relies on clinical experience, diagnostic sensitivity of myocardial biopsy is limited by the segmental nature of disease,[3] and echocardiography's performance is significantly less compared to CMR in detecting abnormalities fulfilling the 2010 TFC.[7]

In both these presented cases, CMR was not performed, which may have impacted our ability to fully appreciate the structural phenotype in these individuals. The improved availability in recent years of CMR has made the detection of ACM with a subtler phenotype possible. Based on this information and our clinical experience, we strongly suggest a comprehensive CMR be performed in the work-up of a patient with presumed IVF and used for evaluation of ACM diagnosis in suspected cases.

Progressive disease

ACM is a progressive disease,[8] and its disease course in desmosomal mutation carriers is well studied.[9] A long-lasting

Table 1 Overview of Task Force Criteria fulfilled per case

	Case 1		Case 2	
	Initial evaluation	Follow-up period	Initial evaluation	Follow-up period
1994 TFC				
Major criteria	1 QRS duration > 110 ms	1	-	1 Severe segmental dilatation of RV
Minor criteria	1 VT with LBBB morphology	2 Negative T waves in V_1–V_3	1 VT with LBBB morphology	1
Diagnosis	No diagnosis	ACM	No diagnosis	ACM
2010 TFC				
Major criteria	1 VT with LBBB morphology and superior axis	2 Negative T waves in V_1–V_3	-	1 Regional akinesia and PLAX RVOT > 32 mm
Minor criteria	1 Prolonged TAD	1	2 Negative T waves in V_4–V_6; VT with LBBB morphology	2
ACM diagnosis	Borderline	Definite	Possible	Definite

ACM = arrhythmogenic cardiomyopathy; LBBB = left bundle branch block; PLAX = parasternal long axis; RV = right ventricle; RVOT = right ventricular outflow tract; TAD = terminal activation duration; TFC = Task Force Criteria; VT = ventricular tachycardia.

asymptomatic phase precedes the clinical phase in most ACM patients, in which electrical abnormalities tend to precede detectable structural changes. Moreover, presence of both an electrical and structural substrate identifies patients at high risk for arrhythmic events.[10]

Accordingly, diagnosis of ACM according to the 2010 TFC is based on electrical, structural, genetic, and histologic abnormalities[3] and requires extensive diagnostic testing and periodic reevaluation in suspected cases. In case 1, right precordial T-wave inversion and echocardiographic RV dilatation after 10 years of follow-up are indicators of disease progression, facilitating ACM diagnosis.

Misinterpretation of initially available data

Our knowledge of the underlying disease process and associated pathogenic mutations has facilitated diagnosis of more subtle and heterogeneous clinical presentations of ACM. Retrospectively, subtle abnormalities could be misinterpreted during initial evaluation, as is illustrated by both our cases.

In both patients, pathogenic mutations were found in nondesmosomal genes. The involvement of nondesmosomal genes in ACM has become clearer in recent years. For example, overlap of desmosomal and sodium channel disease (eg, ACM and Brugada syndrome) is an emerging area of interest (as described in case 1)[11]; the phospholamban gene mutation found in case 2 is associated with both an arrhythmogenic and dilated cardiomyopathy phenotype.[12]

In case 2, increased awareness for biventricular/left-dominant forms in the new 2010 TFC and the availability of molecular genetic testing facilitated the diagnosis during follow-up. In case 1, already at baseline, abnormal wall motion in the subtricuspid region was noted, which was falsely interpreted as tricuspid valve prolapse. Since the subtricuspid region is a hotspot region for early structural changes in ACM,[13] overt ACM was likely already present, albeit not recognized.

Conclusion

VF may be the first clinical manifestation of ACM, as shown in this report. Appropriate diagnosis at later disease stages may be due to (1) improvement in diagnostic tools, (2) disease progression, or (3) misinterpretation of initially available data. In a VF survivor, a specific ACM diagnosis may be clinically less relevant for the index patient. However, in family members, a correct diagnosis may pave the way for cascade screening as a first step toward arrhythmic risk stratification. To detect affected family members before occurrence of ventricular arrhythmias and sudden death, periodic reevaluation of suspected ACM cases during follow-up is important.

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