

Case Report

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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We describe the case of a 51-year-old woman with a 10-year history of dyspnoea and fatigue on slight effort, presyncopal episodes, and ventricular extrasystolic arrhythmia. Tests were negative for coronary artery disease, valvular disease, or left ventricular dysfunction. The patient fulfilled the clinical criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and the diagnosis was confirmed histologically with an endomyocardial biopsy. During 5-year follow up she also exhibited significant structural progression to the left ventricle. This is a rare case of ARVC/D manifested in middle age, with a negative family history, negative test for desmosome mutations, and negative myocardial immunohistochemical analysis, evidence that tends to suggest an acquired form of the disease. We also present a brief review of the clinical, electrocardiographic, structural, pathological/anatomical and genetic characteristics of the disease, the diagnostic criteria, prognosis, management, and sudden death prevention, as well as the way we have managed our patient until the present day.

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Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a primary disease of the myocardium that is characterised by structural abnormalities of the right ventricle and is manifested in the form of ventricular arrhythmias, heart failure and sudden death. In 50% or more of cases the disease is hereditary. Inheritance is autosomal dominant with incomplete penetrance, but there are forms with autosomal recessive inheritance, such as Naxos disease, which has a characteristic cutaneous phenotype.^{1,2} From the pathological and anatomical point of view, ARVC/D is characterised by progressive replacement of the right ventricular myocytes by fibrous or fibro-fatty tissue.³ It is manifested during or after puberty (in 80% of cases before the age of 40 years), with symptoms that vary from palpitations to syncope or sud-

den death, which may be the first sign of the disease. In advanced stages it may lead to right heart failure.⁴ It is attributable to mutations in the desmosomal proteins of the myocardium (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2 and desmocollin-2) that lead to lesions in the connections between myocardial cells, cell death and replacement by fibro-fatty tissue, resulting in dilation, thinning and hypokinesia/dyskinesia of the right ventricular wall, while the trabecular zone shows compensatory hypertrophy.⁵ Under conditions of mechanical stress, the thinner sections of the right ventricle are affected earlier, especially the posterior wall, the outflow tract, and the apex (the "triangle of dysplasia").^{6,7} The disease extends from the subepicardial to the subendocardial strata of the myocardium. The myocardial fibres that are within the zones of fibro-

fatty tissue form a slow-conduction substrate that is susceptible to ventricular arrhythmias with a re-entry mechanism.⁴

Case presentation

A 51-year-old woman, with no risk factors for coronary artery disease, presented with primary complaint dyspnoea and fatigue on slight effort. At the age of 36 she had undergone surgery and radiotherapy for laryngeal cancer.

Her current disease had started 10 years previously, when she first experienced dyspnoea on slight effort. The ECG showed biphasic or negative T-waves in leads I, II, III, aVF and in precordial leads V₁-V₆, which were not present on her ECG from 20 years earlier. Echocardiography revealed a small degree of mitral valve prolapse without regurgitation. A maximal stress test was negative for ischaemia and showed no arrhythmias at 10 min. During the next 7 years she had occasional episodes of presyncope, palpitations, and dyspnoea on slight effort, of varying severity. Three years before her latest admission she experienced constrictive epigastric and retrosternal pain, dyspnoea, nausea and presyncope on vigorous effort. The ECG was similar to the previous one and in addition showed ventricular extrasystoles with a left bundle branch block (LBBB) morphology. Laboratory examinations, including C-reactive protein (CRP) and immunological tests, were within normal limits. Echocardiographic findings were similar to before. A Holter recording gave no notable findings and the stress test was again negative for ischaemia and without arrhythmias. On myocardial scintigraphy, perfusion was uniform and homogeneous (negative for ischaemia). After a new episode of precordial pain with dyspnoea, the patient underwent coronary angiography, on which no angiographically significant stenoses were found. The patient was referred to our department for further investigation of the dyspnoea and fatigue on slight effort.

On clinical examination heart sounds were normal, with no murmur. Pulse was regular, with extrasystoles, and blood pressure was 95/60 mmHg. Breath sounds were normal with no additional sounds.

The ECG (Figure 1) showed low potentials in the limb leads and slow progression of the R-waves in the precordial leads. The QRS complex was of normal width (90 ms in leads V₁ and V₂) and no epsilon waves (low-amplitude signals between the end of the QRS and the onset of the T-wave) were seen.

There were repolarisation abnormalities with inverted T-waves in leads V₁-V₆ (flattening on V₁ and more deeply negative in V₄-V₆), as well as in leads II, III and aVF. Frequent ventricular extrasystoles were recorded with an LBBB morphology and a superior axis, suggesting that their origin was from the posterior wall of the right ventricle.

On the echocardiogram (Figure 2), the left ventricle had normal dimensions (end-diastolic diameter 4.6 cm, end-systolic diameter 3.1 cm) with wall thickness 0.7 cm and systolic function in the lower normal range (ejection fraction, EF 55%). A small degree of hypokinesia and extensive trabeculation of the inferolateral wall were observed, but did not fulfil the diagnostic criteria for left ventricular non-compaction. The right ventricle was slightly dilated (outflow tract diameter in the parasternal long-axis view 34 mm, inflow tract diameter in the 4-chamber apical view 35 mm). There were dyskinetic regions with microaneurysms in the inflow tract, posteroseptal wall, outflow tract, and apex of the right ventricle, above the moderator band. There was also intense trabeculation at the apex and thickening of the moderator band.

The above findings suggested the diagnosis of ARVC/D. There was also moderate tricuspid valve regurgitation without any notable increase in right ventricular systolic pressure (about 30 mmHg). The E/A ratio of transmitral flow was >1 and the deceleration time was 200 ms. Tissue Doppler examination of the right ventricular free wall showed that both systolic and early diastolic velocity were reduced (Sa 8.68 cm/s, Ea 5.65 cm/s), while late diastolic velocity was within normal limits (Aa 8.77 cm/s) and the Ea/Aa ratio was abnormal (<1).

Magnetic resonance imaging (MRI) showed that the left ventricle had normal end-diastolic and end-systolic volumes, a homogeneous signal and focal hypokinesia of the apex and posterior-inferior wall. The right ventricle was estimated visually to be of normal size, with an inhomogeneous signal and dyskinesia of the free and basal anterior wall of its outflow tract. On delayed imaging after gadolinium administration there was no signal enhancement compatible with scar.

Twenty-four hour Holter monitoring recorded >1000 ventricular extrasystoles, 6 pairs and 1 salvo of non-sustained ventricular tachycardia (5 systoles). The signal-averaged ECG was positive for late potentials, with filtered QRS duration (QRSf) 99 ms, low amplitude signal (LAS) duration 41 ms, and root-mean-square (RMS) voltage in the final 40 ms 19 μ V.

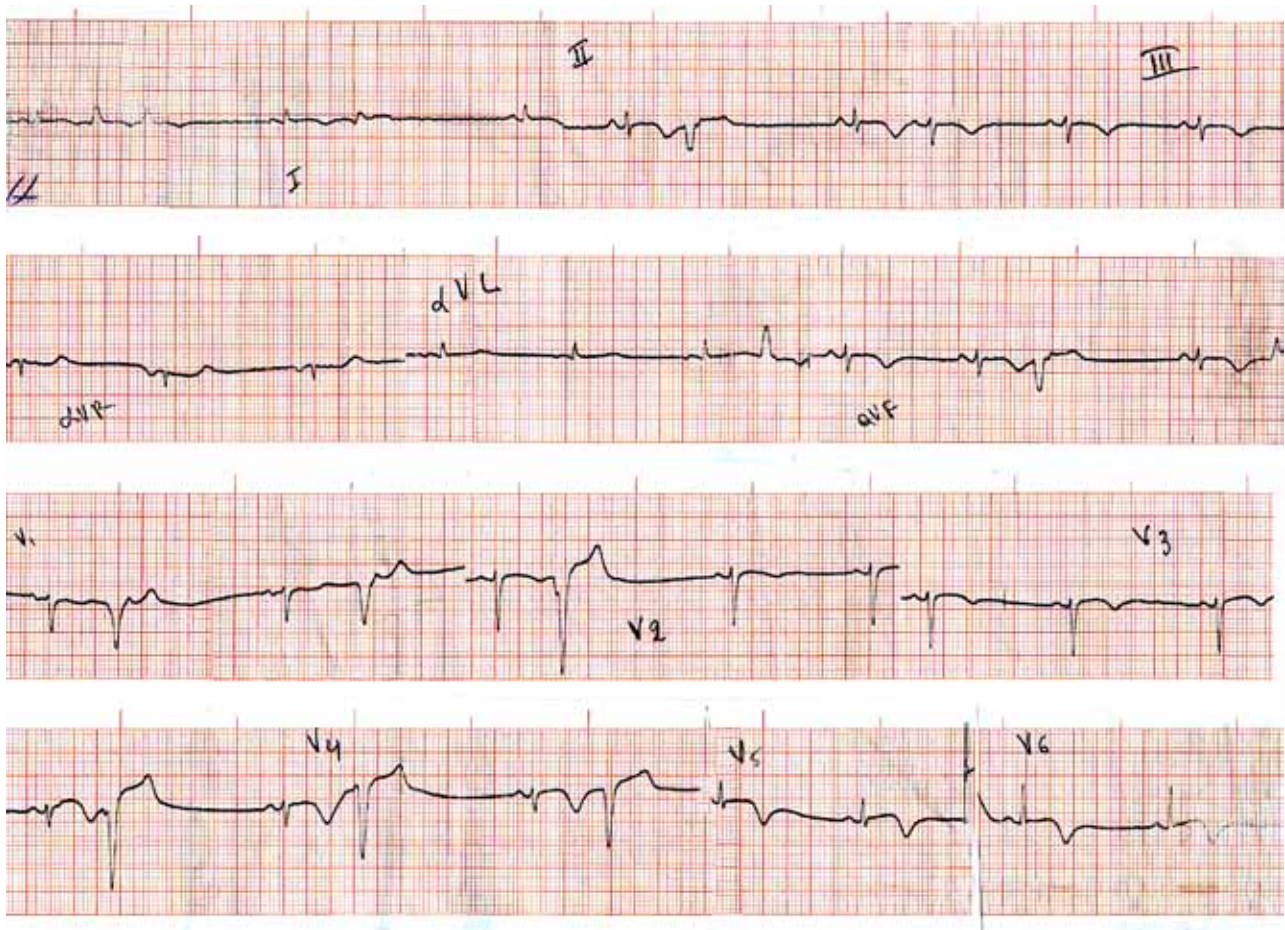


Figure 1. ECG showing low potentials with slow progression of the R-waves in the precordial leads and normal width of the QRS complex. Negative T-waves in the inferior and all precordial leads (deeper in V₄-V₆). Frequent ventricular extrasystoles with left bundle branch morphology and superior axis.

Cardiopulmonary treadmill exercise testing with the Dargie protocol was stopped at 12 min 30 s (6.5 METs) because of muscle fatigue. The patient did not experience angina and the ECG did not show ischaemic changes. She had scattered monomorphic ventricular extrasystoles at rest and during exercise. Maximum oxygen consumption was 21.3 ml/kg/min (Weber class A), showing slight deterioration of the functional capacity of the cardiopulmonary system (NYHA class II).

Based on these findings the patient was judged to fulfil one major and three minor criteria for the diagnosis of ARVC/D: the existence of localised right ventricular aneurysms (major); T-wave inversion in leads V₂-V₃ (minor); positive for late potentials (minor); and non-sustained ventricular tachycardia, as well as ventricular extrasystoles with LBBB morphology, more than 1000/24 h (minor).

There was no other known case of ARVC/D in

the patient's family, nor any case of sudden death. The patient did not originate from Naxos, or the Cyclades more generally, and did not have a Naxos disease phenotype. The history, ECG and echocardiographic examination of her 2 sons (aged 21 and 23 years) showed no findings indicative of the disease. The genetic check of the patient and her children was negative for mutations of plakoglobin, desmoplakin, plakophilin-2, desmocollin-2 and desmoglein-2.

The patient was monitored regularly, under medication with sotalol 80 mg and ramipril 1.25 mg daily, the doses that her low heart rate (50-55 /min) and low blood pressure (systolic 90-100 mmHg) allowed. During the 5 years of the subsequent follow up there was no change in her clinical picture nor any syncopal episode. During the fourth year, Holter monitoring recorded an episode of non-sustained ventricular tachycardia at a rate of 105 /min. It was recommended that the patient undergo an electrophysiological study, but

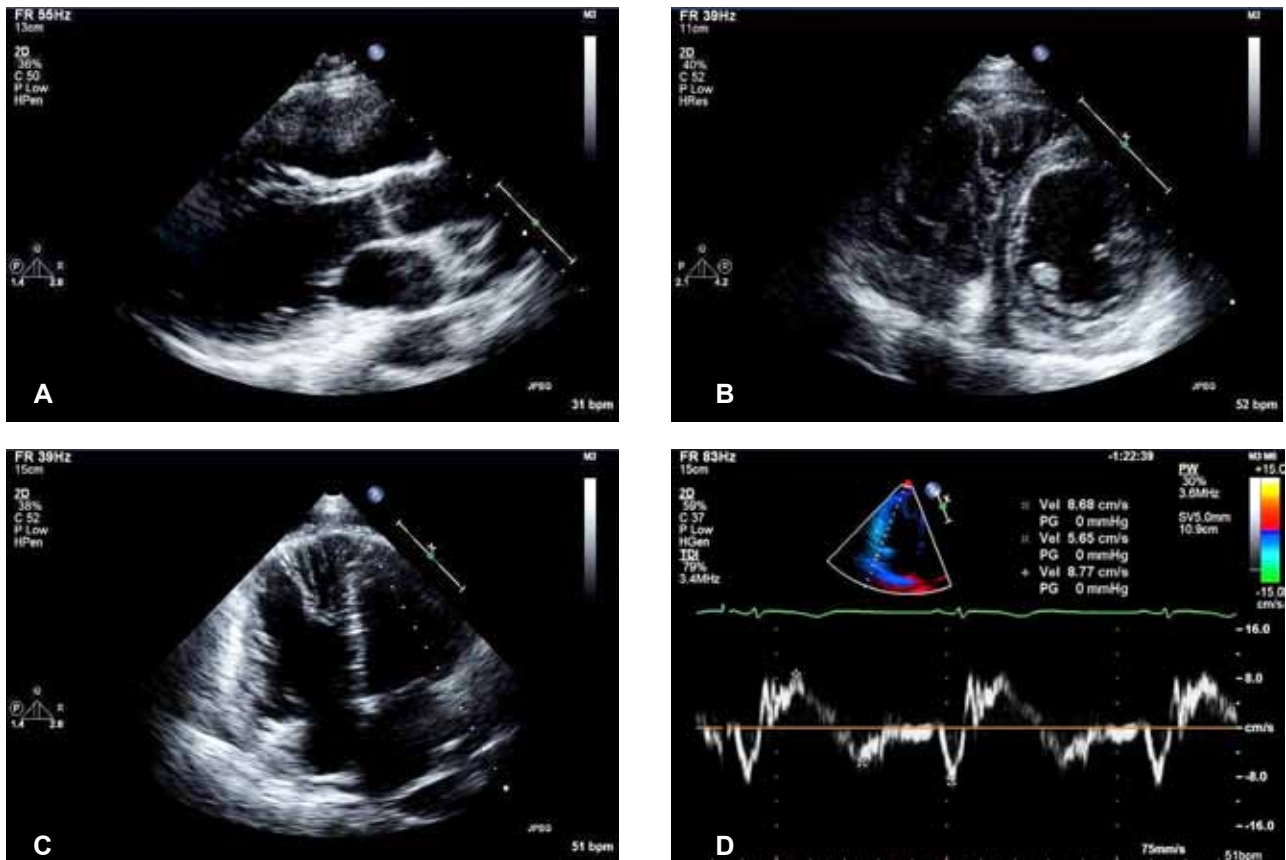


Figure 2. Two-dimensional echocardiogram showing a dilated right ventricle with regions of reduced thickness and an aneurysm at the apex above the moderator band. Intense trabeculation at the apex and thickening of the moderator band. Tissue Doppler shows early diastolic velocity less than late diastolic velocity ($E_a < A_a$).

she declined. In the fifth year her ECG showed a loss of potentials (R) in leads V_5 - V_6 . Echocardiography revealed a significantly compromised left ventricle with EF 35-40% and akinesia of the inferior-posterior wall. The right ventricle was significantly dilated, with thinning of the free wall, microaneurysms in the walls, increased trabeculation, and dilation of the tricuspid annulus. A new MRI examination showed mild left ventricular dilation, with EF 49%, thinning and dyskinesia of the apex, and hypokinesia of the inferior and inferolateral wall. The right ventricle was dilated (end-diastolic volume 134 ml, 84 ml/m^2) with a moderately severe degree of reduction in systolic function (EF 39%), dyskinesia of the outflow tract, and akinesia/dyskinesia of the lower part of the free wall. Delayed contrast imaging showed focal signal enhancement throughout the thickness of the myocardial wall at the left ventricular apex and the mid-myocardial layer of the basal section of the inferolateral wall. In addition, there was signal enhancement in the inferior section of the right ventricular free wall.

Because of the progression of the disease in both ventricles, with the left ventricle severely affected at this stage, defibrillator implantation was recommended. During the implantation, myocardial biopsies were taken from the afflicted right ventricular apex. The histological picture was absolutely compatible with ARVC/D, with extensive loss of myocardial fibres (>60%), replaced mainly by fibrous tissue, the presence of scarce adipocytes and a few inflammatory cells, while the myocardial cells had abnormal dissymmetric and dysmorphic nuclei. No granulomas or giant cells, pathognomonic for sarcoidosis, were observed (Figure 3). Furthermore, the remaining tests for sarcoidosis (chest X-ray, serum angiotensin-converting enzyme, calcium, phosphorus, alkaline phosphatase, erythrocyte sedimentation rate, CRP) were negative. The biopsy material was also sent for immunohistochemical analysis, in which the plakoglobin signal in the intercalated discs was normal (negative for ARVC/D; Figure 4).

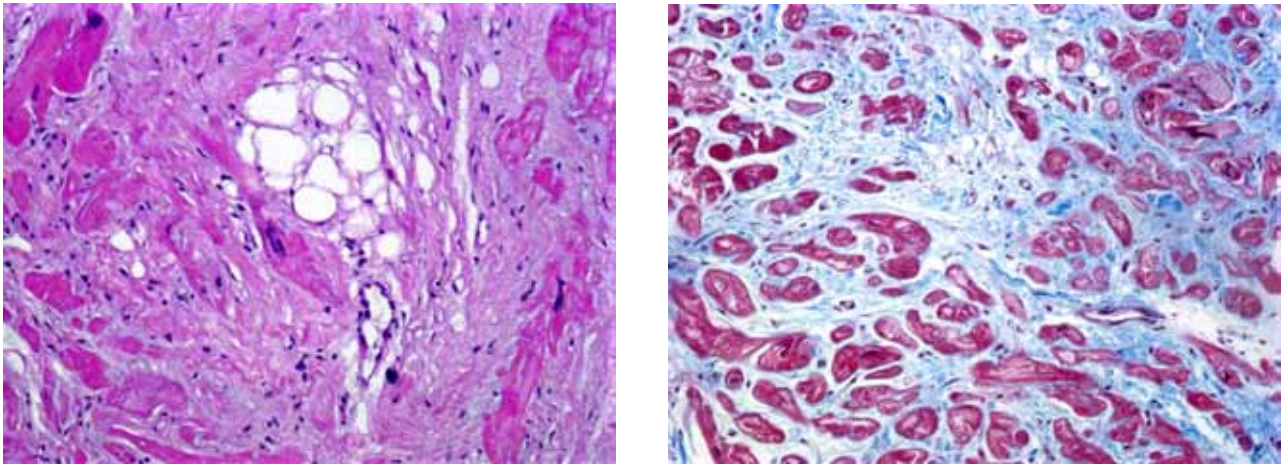


Figure 3. Histological image of the right ventricular myocardium from the endomyocardial biopsy material (3-1: haematoxylin-eosin, 3-2: trichrome stain). Extensive (>60%) loss of myocardium with fibrous replacement, rare fatty and a few inflammatory cells, while the myocardial cells have abnormal dissymmetric and dysmorphic nuclei.

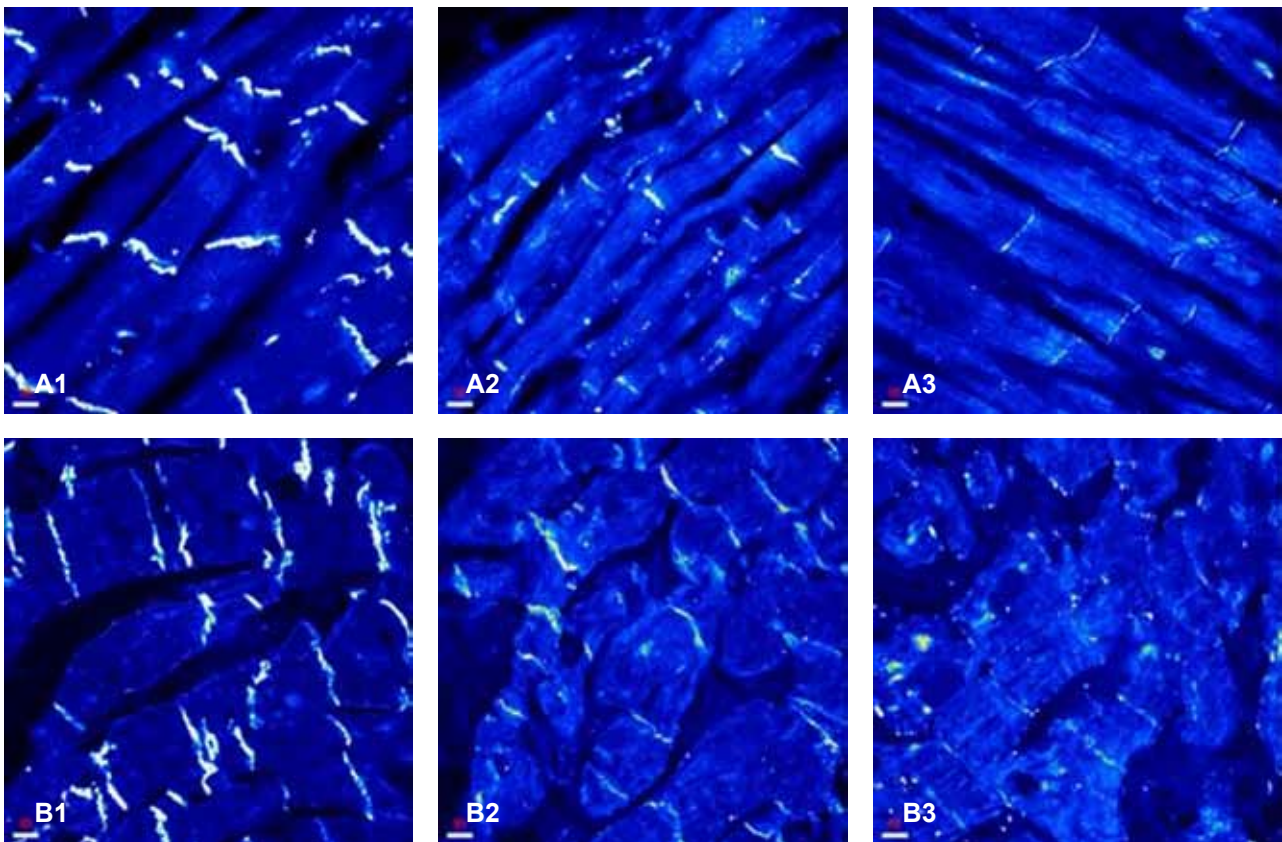


Figure 4. Immunohistochemical analysis, where the plakoglobin and connexin-43 signal in the intercalated discs is normal. Series A: healthy control; Series B: sample from patient; A1 and B1: N-cadherin; A2 and B2: plakoglobin; A3 and B3: connexin-43.

After defibrillator implantation the patient showed no further episodes of ventricular tachycardia. However, she did experience episodes of symptomatic

atrial fibrillation, so the sotalol was replaced by amiodarone and carvedilol, and warfarin was added to her medication.

Discussion

The incidence of ARVC/D in the general population ranges from 1/1000 to 1/50,000, with wide geographic variability. The disease appears to represent a significant cause of sudden death in young people aged <35 years, especially in athletes.³

The natural history of the disease includes 4 phases.^{6,8} In the first, “concealed” phase, the patients are usually asymptomatic, but may be at risk of sudden death, especially during exercise. The structural changes, when present, are of small extent and may be confined to a single region of the “triangle of dysplasia”. In the second, “overt” phase, symptomatic ventricular arrhythmias are observed, while the morphological and functional changes in the right ventricle are more apparent. The third phase is characterised by diffuse damage to the right ventricle, while left ventricular function is preserved by comparison. In the fourth, advanced phase, there is severe, diffuse biventricular involvement, with a phenotype that resembles that of dilated cardiomyopathy.^{6,8,9}

The diagnosis is based on the criteria set down in 1994 by the European Society of Cardiology and the International Society and Federation of Cardiology.¹⁰ The genetic, electrocardiographic, arrhythmologic, structural and histological features of the disease were classified into major and minor criteria. The presence of 2 major, 1 major and 2 minor, or 4 minor criteria from the various categories sets the diagnosis with high specificity, but low sensitivity. For first-degree relatives of patients with ARVC/D (who have a 50% probability of carrying the mutation) modified criteria have been proposed, since in those individuals a single criterion for ARVC/D may represent an expression of the disease.¹¹ At the beginning of 2010 a proposed modification of the diagnostic criteria was published that incorporates new knowledge and technologies and includes quantitative parameters for imaging studies, to improve the diagnostic sensitivity while maintaining the specificity.¹²

For the detection of the structural and functional abnormalities the echocardiogram is the most useful and widely used method. The dimensions of the right ventricle are increased, and the fractional change in the area of the right ventricle is <32% in 66% of patients. The outflow tract diameter is >30 mm in 90% (86% specificity), while regional wall motion abnormalities of the right ventricle are seen in 80%. Trabeculation abnormalities are observed in 54% and the moderator band is hyper-reflexive in 34%. Aneurysms are found in 17% of cases.¹³ On tissue Doppler

imaging, the early diastolic velocity, Ea, is reduced, while the Aa velocity remains unchanged.¹⁴

In a genotyped ARVC/D population of families from Greece and Cyprus (mutations of plakoglobin and plakophilin-2), which is most representative of the clinical spectrum of the disease, the following findings were recorded:¹⁵

- The resting ECG was abnormal in >90%, with the main finding being T-wave inversion in leads V₁-V₃.
- Epsilon waves (small, narrow waves in the final phase or after the end of the QRS complex in the precordial leads, or more rarely the inferior leads), which are specific to the disease, were noted in one third of cases.
- The echocardiogram revealed structural and functional abnormalities of the right ventricle in 100% of patients and of the left ventricle in up to 23%.
- The main echocardiographic finding was regional right ventricular wall-motion abnormalities (100%), while dilation of the right ventricular outflow tract (>33 mm) or the inflow tract (>40 mm) was found in up to 58% of cases.
- Right ventricular aneurysms (akinetic or dyskinetic regions with diastolic bulging), which are specific to the disease, were found in approximately 60%.¹⁵

Late potentials are abnormal in 58-74% and are associated with an increased risk of arrhythmias.¹²

MRI can be used to detect fatty infiltration of the myocardium, wall thinning, and regional abnormalities of right ventricular wall motion. However, the method has serious limitations. Epicardial fat is normally present in the atrioventricular groove and in the anterior apical wall of the right ventricle, and indeed 50% of healthy elderly individuals have fatty infiltration (non-specific finding). In one study, of 46 patients who were considered to suffer from ARVC/D, with the criterion of fatty infiltration and wall thinning on MRI, none finally had the disease, while the findings were not confirmed on a repeat examination.¹⁶ In another study of 29 healthy individuals, MRI was positive for morpho-kinetic abnormalities of the right ventricle, compatible with ARVC/D, in 93% (dyskinesia 76%, hypokinesia 38%).¹⁷ Delayed-enhancement contrast MRI can detect fibrous tissue. The method is positive in two thirds of patients with ARVC/D and a good correlation has been found with histopathology, the degree of right ventricular dysfunction, and the induction of ventricular tachycardia in an electrophysiological study.¹⁸

Myocardial biopsy is diagnostic when <60% myocytes are found, with replacement by fibrous tissue in the right ventricular free wall, with or without fatty tissue.¹² A false negative result may be associated with the absence of involvement of the interventricular septum (from where the samples are usually taken), with the segmental (“patchy”) nature of the disease (even when the samples are taken from the right ventricular free wall where the changes are typically located), or with the fact that the involvement, at least in the early stages, is localised only in the subepicardial layers of the myocardium. In biopsies from the free wall, the sensitivity approaches 80%, with 92% specificity. Sampling from the free wall entails a risk of perforation.¹⁹

It was recently found that, in the immunohistochemical analysis of a sample of cardiac tissue, the plakoglobin signal in myocardial cell connections was significantly reduced in patients with ARVC/D, while it was strongly positive in healthy controls and in those suffering from dilated or hypertrophic cardiomyopathy, or heart failure of ischaemic aetiology.²⁰ Using this method, a correct diagnosis was made in 10 of 11 cases of certain (by clinical criteria) ARVC/D, while the diagnosis of ARVC/D was correctly ruled out in 10 of 11 cases without ARVC/D (sensitivity 91% and specificity 82%). The plakoglobin signal is reduced, not only in the affected regions of the right ventricle with typical changes and replacement by fibro-fatty tissue, but also in regions that appear normal, as well as in the left ventricle, the interventricular septum, and the subendocardium of those regions. These observations suggest that taking biopsies from regions with structural changes might not be necessary for the diagnosis of ARVC/D.²⁰ However, in our patient the histological examination was typical for ARVC/D and the immunohistochemical analysis was negative. Cases of ARVC/D with a negative immunohistochemical analysis are relatively rare, and concern sporadic cases of the disease with a negative genetic examination for desmosome mutations, as in our patient. Such cases probably represent an “acquired” form of ARVC/D.

In mild forms of ARVC/D, without clear structural abnormalities of the right ventricle, differential diagnosis is required to rule out other arrhythmogenic conditions with a structurally normal heart, such as ventricular tachycardia from the right ventricular outflow tract, catecholaminergic ventricular tachycardia, and Brugada syndrome. In severe forms of ARVC/D with diffuse involvement of both ventricles differ-

ential diagnosis from dilated cardiomyopathy is required. Cardiac sarcoidosis may mimic ARVC/D absolutely as regards the clinical characteristics (electrocardiographic, structural, arrhythmologic) and the final diagnosis may require endomyocardial biopsy. The differential diagnosis between ARVC/D and cardiac sarcoidosis is necessary in sporadic cases of ARVC/D, especially when the left ventricle is also involved.²¹ A search for *erythema nodosum*, haematological tests (serum angiotensin-converting enzyme, serum calcium and phosphorus, alkaline phosphatase, erythrocyte sedimentation rate, CRP), and a chest X-ray can assist in the diagnosis (protocol of the “Yannis Protonotarios” Medical Centre, Naxos). In our patient, the test for sarcoidosis, including the myocardial biopsy and MRI (lack of septal involvement and findings from the lungs and mediastinum to support sarcoidosis) was negative.

In the USA, of 100 cases of ARVC/D, 69% were diagnosed while the patient was living. Half the patients were asymptomatic until the age of 35 years. In 50% the first manifestation of the disease was malignant or potentially malignant arrhythmia (26% syncope, 23% sudden death). Progression to heart failure was unusual (10%).²²

For patients with a history of ventricular tachycardia, the risk of death ranges in various publications from 0.08%²³ to 4%^{24,25} annually. An increased risk of sudden death is present in patients with ARVC/D and a history of cardiac arrest, or haemodynamically unstable ventricular tachycardia, those with recurrent syncopal episodes, or left ventricular involvement, younger patients, and those with QRS dispersion ≥ 40 ms.²⁴⁻²⁷ In the study mentioned above from Greece and Cyprus, with a genotyped ARVC/D population, QRS dispersion ≥ 40 ms was associated with an increased risk for non-fatal arrhythmic events (syncope, sustained ventricular tachycardia), but not for sudden death. Left ventricular involvement showed a trend towards correlation with sudden death.¹⁵ Patients with Naxos disease have a worse prognosis. In one study, at 10-year follow up, 62% of patients showed structural progression of the disease in the right ventricle, while 27% progressed to heart failure; 46% exhibited symptomatic ventricular arrhythmias and the annual cardiac mortality was 3% (sudden death 2.3%).²⁸

An electrophysiological study does not appear to be of particular benefit for risk stratification and the data are conflicting. In a study by Corrado et al,²⁶ of 132 patients who received a defibrillator 111 had previously undergone an electrophysiological study and

sustained ventricular tachycardia had been induced in 98. The positive and negative predictive values of the electrophysiological study for appropriate device discharges were only 49% and 54%, respectively. In contrast, an electrophysiological study showed a trend to predict appropriate device activation ($p=0.07$) in a study by Wichter et al,²⁹ and predicted it with statistical significance ($p=0.024$) in a study by Roguin et al.³⁰ According to guidelines, the electrophysiological study may be useful in risk stratification for sudden cardiac death in patients with ARVC/D (Class IIb, level of evidence C).³¹

Treatment is aimed mainly at the prevention and management of malignant arrhythmias and sudden death. Patients with right or bilateral heart failure should also receive appropriate treatment. In addition, patients should avoid competitive sports and any activity that causes palpitations, presyncope or syncope episodes.²³

Patients who have well-tolerated or non life-threatening arrhythmias have a relatively low risk of sudden death and may be treated with antiarrhythmic medication, guided by Holter monitoring and stress testing or an electrophysiological study.⁸ Sotalol prevented the recurrence of ventricular tachycardia in 68.4% of patients with inducible and 82.8% of patients with non-inducible ventricular tachycardia.³² Antiarrhythmic drugs were examined in all recorded patients with ARVC/D in North America who had received an implantable defibrillator. Neither sotalol nor beta-blockers appeared to provide protection, while in a small number of patients amiodarone showed superiority in the prevention of ventricular arrhythmias.³³

Radiofrequency ablation has a low success rate. This is probably due to the multiplicity of arrhythmogenic foci that are the result of the inhomogeneous nature of the disease, and to its progressive nature, which leads to the appearance of new forms of tachycardia. Ablation may be useful as adjunctive therapy in patients with ARVC/D who have an implantable defibrillator and suffer from frequent recurrences of ventricular tachycardia despite optimum antiarrhythmic medication (guidelines Class IIa, level of evidence C).³¹

Patients with a history of resuscitation from cardiac arrest, or who do not respond to or cannot tolerate antiarrhythmic medication, are candidates for defibrillator implantation.^{22,26,29,30,34,35} There is a clear tendency in recent years to implant a defibrillator for primary prevention in an ever-increasing percentage

of cases.^{26,29,30,34} Defibrillator implantation is recommended for the prevention of sudden cardiac death in patients with ARVC/D who have documented sustained ventricular tachycardia or ventricular fibrillation, are receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year (Class I, level of evidence B).³¹ Defibrillator implantation can be effective in the prevention of sudden cardiac death in patients with ARVC/D who have extensive disease, including those with left ventricular involvement (as in our patient), with 1 or more family members affected by sudden cardiac death, or undiagnosed syncope when ventricular tachycardia or ventricular fibrillation have not been excluded as the cause of the syncope, who are receiving chronic optimal medical therapy and have reasonable expectation of survival with a good functional status for more than 1 year (Class IIa, level of evidence C).³¹

In patients who exhibit electrical storm, the defibrillator may be life-saving but suppression of the arrhythmias with medication is required. In the series reported by Roguin et al, 5 of 42 patients experienced electrical storm and all were treated successfully with sotalol.³⁰

A surgical method of treating the arrhythmias is total disconnection of the right ventricular free wall.³⁶ Its advantage is that it isolates both ventricles from each other. Thus, it limits the myocardial mass that is available for fibrillation and does not permit ventricular tachycardia that starts from the right ventricle to spread to the left. It is followed by acute right ventricular failure, which progressively recovers.³⁷ This method has practically been abandoned as defibrillators have become ever more pervasive.

The first manifestation of the disease in our patient was at the age of 41 years, with atypical – angular type – complaints and repolarisation abnormalities on the resting ECG, followed by episodes probably related to arrhythmia (palpitations and presyncope). At the age of 48 years, further deterioration had occurred, with angina, probable arrhythmic episodes, progression of the repolarisation abnormalities on the ECG, and structural progression of the disease in the right ventricle with extension to the left. This progression of ARVC/D is well known in the literature.^{38,39} The ECG with deeply inverted T-waves in the left precordial and inferior leads is characteristic of left ventricular involvement.^{39,40} The fact that imaging examinations (echocardiogram, MRI) showed only mild findings (over several years) does not indicate slight

involvement, because the pathological process takes place mainly in the subepicardial layers, without usually causing notable wall motion abnormalities.^{39,40} The new structural progression of the disease during the fifth year of follow up in our department (15 years after the start of symptoms), with significant further left ventricular involvement, worsened the prognosis of the disease. The patient was classified as having high risk for sudden cardiac death and for that reason defibrillator implantation was recommended for primary prevention with a Class IIa indication.³¹

The negative genetic examination is not incompatible with the diagnosis of the disease. Mutation of the genes that code for desmosome protein complexes has been detected in 40-43% of sufferers from ARVC/D (using current criteria).^{36,41} In familial ARVC/D, mutation is detected in almost 70% of patients, and in an even higher percentage when there is a family history of early sudden death.³⁶ In patients who fulfil the criteria for the diagnosis of ARVC/D but have a negative genetic examination the appearance of the disease is more sporadic.

As regards the interpretation that the patient's cardiomyopathy was related to the neck radiotherapy she had undergone for cancer of the larynx 17 years before, the shielding applied was thorough and the probability of significant radiation to the chest was judged to be exceedingly low.

Two large registries of ARVC/D cases, the European⁴² and the American (which is under development) are expected to make a major contribution to the determination of the clinical, pathological, anatomical and genetic characteristics of ARVC/D, the evaluation of diagnostic criteria, the determination of protocols for the treatment of the disease, and the prevention of sudden death. The "Yannis Protonotarios" Medical Centre in Naxos is participating in this initiative as a Greek reference centre.

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