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Case Report

REPORT OF AN ATYPICAL CASE WITH ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA OR UHL'S ANOMALY

ATIPICIDADES EN UN CASO CON DISPLASIA ARRITMOGÉNICA DEL VENTRÍCULO DERECHO O ENFERMEDAD DE UHL

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ABSTRACT

Arrhythmogenic right ventricular dysplasia is a cardiomyopathy characterized by malignant ventricular arrhythmias and progressive structural abnormalities, affecting primarily the right ventricle. It appears due to a partial or massive progressive replacement of the myocardium by fibroadipose or adipose tissue. Uhl's disease may be an extreme and widespread manifestation of arrhythmogenic right ventricular dysplasia, a rare congenital disorder with absence of right ventricular myocardium, so that its walls are paper thin. The case of a 56 year old male patient who had loss of consciousness and underwent clinical and echocardiographic diagnosis is presented. The clinical features, diagnosis and action to take against this potentially fatal heart disease in patients with syncope, ventricular tachycardia or cardiac arrest are discussed.

Key words: Arrhythmogenic right ventricular dysplasia, Cardiomyopathy

RESUMEN

La displasia arritmogénica del ventrículo derecho es una miocardiopatía caracterizada por arritmias ventriculares malignas y anomalías estructurales progresivas, que afectan primariamente al ventrículo derecho. Se presenta por una sustitución progresiva parcial o masiva del miocardio por tejido adiposo o fibroadiposo. La enfermedad de Uhl puede ser una manifestación extrema y generalizada de la displasia arritmogénica

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del ventrículo derecho, trastorno congénito muy poco frecuente con ausencia de miocardio ventricular derecho, por lo que sus paredes son delgadas como el papel. Se comenta el caso de un paciente masculino de 56 años que presentó pérdida de conocimiento y se le realizó el diagnóstico clínico y ecocardiográfico. Se discuten las características clínicas, el diagnóstico y la conducta a seguir ante esta cardiopatía potencialmente letal en pacientes que sufren síncope, taquicardia ventricular o parada cardíaca.

Palabras clave: Displasia Ventricular Derecha Arritmogénica, Cardiomiopatía

INTRODUCTION

The arrhythmogenic right ventricular dysplasia (ARVD) is a cardiomyopathy characterized by progressive structural abnormalities affecting primarily the right ventricle (RV) which produces ventricular arrhythmias[1,2]. This rare disorder was described by Fontaine et al.[3] in 1977. The overall prevalence is difficult to estimate, since many cases are diagnosed postmortem, however, it is the cause of 3 to 4% of deaths in athletes, and 5% of all sudden deaths before 65 years of age[4]. Myocardial degeneration may extend to the interventricular septum and the left ventricle, especially in advanced stages of the disease[5]. ARVD may occur in sporadic and familial forms. The familial predisposition was described in 1982 by Marcus et al.[6-7], about 30% of patients diagnosed relate family history[4,8] and several responsible genetic alterations have been identified. The disease is characterized by progressive partial or massive replacement of the myocardium by adipose or fibrofatty tissue. This infiltration is a substrate for electrical instability and leads to various arrhythmias, ranging from isolated premature ventricular contraction to stable ventricular tachycardia (VT) or ventricular fibrillation (VF)[2,5,9]. Uhl's anomaly may be an extreme and widespread manifestation of ARVD, and it is a rare congenital disorder with absence of right ventricular myocardium, so that its walls are paper thin[7-8,10]. Gaffney et al.[11] state that Uhl's anomaly and ARVD could be manifestations of a single and presumably congenital pathological process: parchment RV syndrome[11].

Echocardiography is a noninvasive technique and it is the first-line method for evaluating patients with suspected diagnosis of dysplasia and for family screening[12]. Diagnosis of ARVD is based on a combination of major and minor criteria[13].

The case of a patient who was diagnosed in the Cardiosurgical Intensive Care Unit and who had been admitted for syncope is described. This case was published in the Argentinean Federation of Cardiology Journal[10] in the Images in Cardiology section, but due to its importance and relevance it has also been decided to present it as a Case Report.

CASE REPORT

The unusual case of a 56-year-old male with pathological family history of premature sudden death (<35 years), personal history of palpitations, fatigue, atypical chest pain and several episodes of syncope triggered by exercise (the first manifestations began between 15 and 35 years) is discussed. The reason for his admission to the Cardiosurgical Intensive Care Unit was syncope preceded by palpitations, but he denied having chest pain or dyspnea. On physical examination, the patient was eupneic, hypotensive and tachycardic (BP 75/55 mmHg and heart rate of 160 per minute) with peripheral oxygen saturation of 97% (in environmental air), and filiform peripheral pulses with mild jugular venous distension. Cardiac auscultation revealed an arrhythmic and very tachycardic heart, and it seemed like the presence of a fourth heart sound with muffled heart sounds. Pulmonary auscultation was normal, and tympanic abdomen was diffuse, tender in upper quadrants, and no signs of peritoneal irritation; a painful hepatomegaly of about 3 cm was evident, with a predominance of the right lobe. The lower limbs showed a mild edema. Hematological and biochemical tests showed no significant alterations. The chest x-ray showed an enlarged heart with predominance of right cavities. The electrocardiogram (ECG) showed a stable VT with left bundle of His branch block, and an undetermined QRS axis, without signs of acute myocardial ischemia. The transthoracic echocardiogram showed the presence of a dilated right ventricle with severe systolic dysfunction and right ventricular ejection fraction (RVEF) <30% as determined by the method of Simpsom (Figure 1). Also, dyskinetic areas and regional aneurysms in the RV with increased telediastolic diameter were noted. Ventricular morphology recalls onionskin and RV is known as parchment RV. Ventricular arrhythmia was reversed with a pharmacologic cardioversion (amiodarone), to improve his hemo-

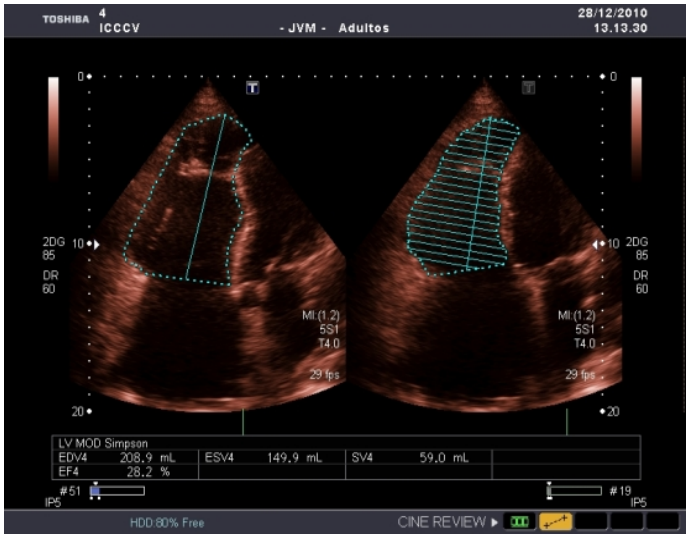

Figure 1. Transthoracic echocardiography. Apical 4-chamber view. Determination of right ventricular function RVEF <30% (Simpsom Method). Image taken, with permission, from Rev Fed Arg Cardiol. [2012; 41(1): 59-60][10].

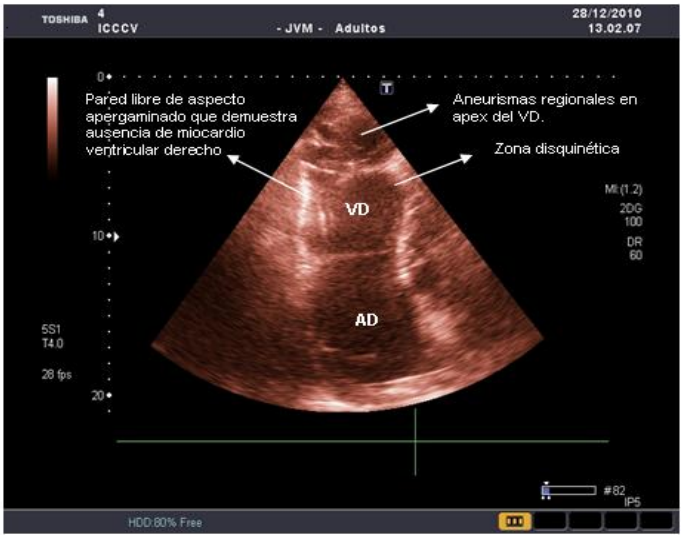

Figure 2. Transthoracic echocardiography. Apical view. No RV myocardium, parchment-like walls where regional aneurysms and dyskinetic areas are shown in the apex. VD, right ventricle, AD: right atrium. Image taken, with permission, from Rev Fed Arg Cardiol. [2012; 41(1): 59-60][10].

dynamic status. Volume therapy was administered without a proper response in blood pressure, so vasopressor and inotropic therapy was started. The patient remained hypotensive and died of circulatory shock 12 days after admission.

The pathological study could not be performed because the family did not give consent. The case was concluded as ARVD or Uhl's anomaly, according to Marcus et al. criteria[13].

DISCUSSION

ARVD is a cardiomyopathy whose fundamental structural anomaly is the right ventricular myocardial degeneration, which in advanced stages of the disease may spread to the left ventricle. The prevalence of ARVD in the general population has been estimated at values ranging from 1/2.000 to 1/10.000. 80% of cases are diagnosed in patients younger than 40 years. It should be suspected in all young patients with an apparently normal heart that suffer syncope, VT or cardiac arrest[5].

ARVD is an inherited disorder. There is a clear familial incidence (30-50% of cases), with an autosomal domi-nant transmission pattern, varying degrees of penetra-tion and polymorphic phenotypic expression. An autosomal recessive form has also been described[7].

The first mutation causing nonsyndromic ARVD was described by Rampazzo et al.[14] in 2002. Such mutation was identified in the desmoplakin gene, which encodes a desmosome component. In 2004, Gerull et al.[15] described 25 mutations of the cardiac desmosomal gen of plakophilin 2. Desmosomal dysfunction is currently considered the common final pathway in ARVD pathogenesis. Different genetic variants of ARVD have been located in the chromosomal map and over 140 mutations that cause the disease have been described, most of them corresponding to genes encoding desmosomal proteins[15]. The integrity of desmosomes is necessary to maintain the normal function of tight junctions as intercellular channels responsible for electric coupling and signaling mechanisms in the regulation of growth, cellular differentiation and development. Genetic mutations, the cause of ARVD, result in an haploinsufficiency and a reduction of desmosomal protein expression, which may predispose to breakage of cell mechanical contacts, possibly triggered by a mechanical tension of the RV (as occurs during exercise or sports activity). Degeneration and death of cardiomyocytes is the anatomic-pathological conse-

quence of these mutations of adhesion proteins with subsequent progressive replacement by adipose and fibroadipose tissue[16].

ARVD should be differentiated from Uhl's anomaly, a very rare congenital disorder with absence of right ventricular myocardium, thus the RV wall is paper thin. James et al. (Circulation, 1996), suggest that Uhl's anomaly and ARVD share a similar pathogenesis. The definitive differential diagnosis could only be confirmed by autopsy[8,10].

ARVD is usually manifested in the form of VT episodes with left bundle of His branch block morphology and has its origin in the RV in apparently healthy adolescents or young adults. Ventricular arrhythmias may be asymptomatic and detected on routine ECG or can cause palpitations, syncope or sudden death. The age at which the first event occurs is between 15 and 35 years. Clinical presentations include palpitations, fatigue, atypical chest pain, syncope and sudden cardiac death. The disorder affects men more often than women, and it usually manifests in them with a broader expression of the disease. Symptomatic heart failure is a rare manifestation of ARVD and most often it occurs in advanced stages of the disease. Patients with a long history of ARVD have an affected left ventricle and suffer from clinical symptoms of biventricular heart failure[8,17].

Diagnosis of arrhythmogenic cardiomyopathy is based on the presence of structural, histological, electrocardiographic, arrhythmic and genetic factors, and on family history. According to the Task Force Report published by McKenna et al.[18] in 1994, patients must meet two major criteria, or one major and two minor, or four minor criteria for them to be considered affected by ARVD. A new modification of diagnostic criteria in order to increase the diagnostic sensitivity has recently been published[19].

The ECG of patients with ARVD typically shows a regular sinus rhythm with QRS duration> 110 ms in lead V_1. Electrocardiographic changes include inverted T waves in the right precordial leads beyond V1, without any right bundle of His branch block and right ventricular late potentials in the form of "epsilon waves" in leads V1-V3. T-wave inversion in these leads is a well-known feature of the ECG in ARVD and in absence of right bundle of His branch block, it has been proposed as a major diagnostic criterion. This variant is present in 1-3% of the healthy population of 19-45 years of age, but occurs in 87% of patients with ARVD. Epsilon waves are "post-excitation" electrical potentials of small amplitude, occurring in the ST segment after the end of the QRS complex. These waves, which are observed in 33% of patients with ARVD, are considered a major diagnostic criterion[19].

The imaging techniques used to diagnose morphofunctional abnormalities consistent with ARVD include conventional angiography, echocardiography, computed tomography, radionuclide angiography and magnetic resonance imaging (MRI). The right ventricular angiography has been historically considered the best imaging for the diagnosis of ARVD and has demonstrated a high specificity (90%). Echocardiography is safe and a first-line method for evaluating patients with suspected ARVD and the screening of family members. MRI can differentiate fat from muscle; it can also make a highly accurate and quantitative assessment of the RV size and function. The sensitivity and specificity of RV intramyocardial fat detection by MRI in the diagnosis of ARVD are variable and range from 22 to 100%. Fat identification can be difficult, because the RV is a thin structure and the affected myocardial areas can be very small. Moreover, it is now well known that the presence of fat in the RV myocardium can be normal [20-22]. Differentiating a pathological fatty infiltration in areas where adjacent epicardial fat is normally present, as in the atrioventricular groove and the anterior-apical RV, can be especially difficult. Isolated areas of fat replacement in elderly patients, with prolonged use of corticosteroids, in obesity, in other cardiomyopathies and on idiopathic VT of the RV outflow tract (RVOT) have also been observed. It has been reported that demonstrating the presence of fibrous tissue has a greater diagnostic importance than finding fat alone[22,23].

The main differential diagnosis of ARVD is the one that should be done with RVOT VT, sarcoidosis, idiopathic dilated cardiomyopathy and isolated myocarditis. Both RVOT VT and ARVD VT occur in apparently healthy young individuals, and both may present with ventricular tachycardia or premature ventricular contraction with left bundle of His branch block and inferior axis. Although it is difficult to diagnose a clear case of ARVD, its differentiation in its early stages with regard to RVOT tachycardia, a generally benign arrhythmic disorder with no family character, remains a real clinical challenge.

The main factors that determine poor evolution are severe right ventricular dysfunction, left ventricular disorder, syncope, young age, male sex, history of cardiac arrest; the rapid and poorly tolerated VT with different morphologies, and familial incidence of youth sudden deaths. Very high-risk patients present clinical signs of right heart failure and may have left ventricular dysfunction and a history of VT[24].

The main objective of therapeutic strategy in ARVD is preventing sudden cardiac death. The three main treatments are antiarrhythmic drugs, catheter ablation and use of implantable cardioverter defibrillator (ICD). ARVD patients with no history of syncope or cardiac arrest, having premature ventricular contraction in pairs or short runs, typically do not have an increased arrhythmic risk and therefore do not require a specific antiarrhythmic therapy. In patients with stable VT, antiarrhythmic drug treatment aims not only at the suppression of VT recurrences, but mainly at the prevention of sudden cardiac death. Sotalol, at doses of 320-480 mg/day, has been identified as the drug with better results, with an overall efficacy rate of 68%. Amiodarone, a class III drug, has shown efficacy in the treatment of malignant arrhythmias[25,26].

Current indications for catheter ablation in patients with ARVD are well tolerated monomorphic VT with localized forms of the disease and refractory to medication, or incessant VT or with frequent ICD discharges. In the latter case, the ablation catheter may play an important role as palliative or adjuvant treatment option for the reduction or suppression of VT[26]. In ARVD, it is the result of a reentry circuit associated with a scar, similar to that observed after myocardial infarction. Catheter ablation with RV voltage maps, using elaboration techniques of conventional or electroanatomic maps can provide favorable short-term results[27].

ICD therapy improves long-term prognosis and survival when applied to a selected high-risk population and as secondary prevention. A frequent complication is due to the progression of myocardial atrophy and subsequent replacement of fat in the electrode implantation site, which results in a loss of perception function of the RV defibrillation electrode, which needs replacement. Thus, the indication for ICD therapy in ARVD should weigh the potential benefits versus complication risks. When the disease has progressed to right ventricular or biventricular failure, the currently prescribed treatment for heart failure should be applied, including diuretics, beta blockers, angiotensin-converting enzyme inhibitors and anticoagulants. In case of refractory right heart failure, heart transplantation may be the only choice[28,29].

The progression of the disease is uncertain and individual for each patient and can cause sudden death in young patients, or constitute a finding in autopsies of elderly patients. Understanding its genetic basis, and its structural and functional characteristics will allow in the future the search for new therapies in the prevention, treatment and monitoring of patients with this rare disease[30].

Conflicts of interest

The authors of this paper declare no conflicts of interest.

REFERENCES

1. Frank R, Fontaine G, Mialet G, Sol C, Guiraudon G, Grosgogeat Y. Electrocardiologie de cas de dysplasie ventriculaire droite arythmogene. Arch Mal Coeur Vaiss. 1978;71(9):963-72.
2. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomiopathy and sudden death in young people. N Engl J Med. 1988;318(3):129-33.
3. Fontaine GH, Guiraudon G, Frank R. Stimulation studies and epicardial mapping in ventricular tachycardia: study of mechanisms and selection for surgery. In: Kulbertus He, ed. Re-entrant arrhythmias: mechanisms and treatment. Baltimore: University Park Press; 1977. p. 334-50.
4. Anderson EL. Arrhythmogenic right ventricular dysplasia. Am Fam Physician. 2006; 73(8):1391-8.
5. Gallo P, D'Amati G, Pelliccia F. Pathologic evidence of extensive left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy. Hum Pathol. 1992;23(8):948-52.
6. Thiene G, Basso C. Arrhythmogenic right ventricular cardiomyopathy: an update. Cardiovasc Pathol. 2001;10(3):109-17.
7. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, *et al*. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65(2):384-98.
8. Thiene G, Corrado D, Basso C. Arrhythmogenic right ventricular cardiomiopathy/dysplasia. Orphanet

J Rare Dis. 2007;2:45.
9. Kayser H, Van der Wall EE, Plein S,Bloomer TN, de Roos A. Diagnosis of arrhythmogenic right ventricular dysplasia: a review. Radiographics. 2002; 22(3): 639-48.
10. Morales Pérez LM, Jerez Castro AM, San Román García E. Displasia arritmogénica del ventrículo derecho o enfermedad de UHL. Rev Fed Arg Cardiol. 2012;41(1):59-60.
11. Gaffney FA, Nicod P, Lin JC, Rude RE. Noninvasive recognition of the parchment right ventricle (Uhl's anomaly arrhythmogenic right ventricular dysplasia) syndrome. Clin Cardiol. 1983;6(5):235-42.
12. Daliento L, Rizzoli G, Thiene G, Nava A, Rinuncini M, Chioin R, *et al*. Diagnostic accuracy of right ventriculography in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 1990;66(7):741-5.
13. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, *et al*. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J. 2010;31(7):806-14.
14. Rampazzo A, Nava A, Malacrida S, Beffagna G, Bauce B, Rossi V, *et al*. Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. Am J Hum Genet. 2002;71(5): 1200-6.
15. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, McDermott DA, *et al*. Mutations in the desmosomal protein plakophilin 2 are common in arrhythmogenic right ventricular cardiomiopathy. Nat Genet. 2004; 36(11):1162-4.
16. Capulzini L, Brugada P, Brugada J, Brugada R. Arritmias y enfermedades del corazón derecho: de las bases genéticas a la clínica. Rev Esp Cardiol. 2010;63(8):964-65.
17. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, *et al*. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomiopathy/dysplasia: a multicenter study. J A Coll Cardiol. 1997;30(6):1521-30.
18. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/ cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J. 1994; 71(3):215-8.
19. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke D, et al. Diagnosis of arrythmogenic right ventricular cardiomyopathy/dysplasia. Proposed modification of the Task Force criteria. Circulation. 2010;121(13):1533-41.
20. Daliento L, Rizzoli G, Thiene G, Nava A, Rinuncini M, Chioin R, et al. Diagnostic accuracy of right ventriculography in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 1990;66:741-5.
21. Van der Wall EE, Kayser HW, Bootsma MM, De Roos A, Schalij MJ. Arrhythmogenic right ventricular dysplasia: MRI findings. Herz. 2000;25(4):356-64.
22. Tandri H, Bomma C, Calkins H, Bluemke DA. Magnetic resonance and computed tomography imaging of arrhythmogenic right ventricular dysplasia. J Magn Reson Imaging. 2004;19(6):848-58.
23. Burke AP, Farb A, Tashko G, Virmani R. Arrhythmogenic right ventricular cardiomyopathy and fatty replacement of the right ventricular myocardium: are they different diseases? Circulation. 1998;97(16): 1571-80.
24. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomiopathy. Circulation. 2004;110:1879-84.
25. Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease: results in patients with inducible and noninducible ventricular tachycardia. Circulation. 1992; 86(1):29-37.
26. Marcus G, Glidden D, Polonsky B, Zareba W, Smith L, Cannom D, *et al*. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomiopathy. J Am Coll Cardiol. 2009;54(7):609-15.
27. Arruda M, Armaganijan TF, Di Biase L, Patel D, Natale A. Catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplsia. J Interv Card Electrophysiol. 2009;25(2):129-33.
28. Wichter T, Brethardt G. Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular cardiomiopathy: a role for genotyping in decision-making? J Am Coll Cardiol. 2005;45(3): 409-11.
29. Hodgkinson KA, Parfrey PS, Bassett AS, Kupprion

C, Drenckhahn J, Norman MW, *et al*. The impact of implantable cardioverter defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomiopathy (ARVD5). J Am Coll Cardiol. 2005;45(3):400-8.

30. Turrini P, Basso C, Daliento L, Nava A, Thiene G, *et al*. Is arrhythmogenic right ventricular cardiomyopathy a pediatric problem too? Images Paediatr Cardiol. 2000; 3(1):18-37.