

Arrhythmogenic right ventricular cardiomyopathy – cause of sudden death in young people

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Abstract: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC) is a heart muscle disease pathologically characterized by progressive fibro fatty replacement of myocytes, initially involving the right ventricle. We report the case of a 21 years-old patient, with no cardiac history, who died suddenly during an intense exercise. The heart was completely examined macroscopically. Full-thickness blocks of myocardium were removed for histologic examination from the right and left ventricles and the ventricular septum. Myocardial sections were stained with hematoxylin–eosin, van Gieson and Masson trichrome dyes. According to gross inspection and histologic examination, the right ventricle disclosed severe replacement of the wall thickness by fibro-fatty tissue except for a subendocardial layer and trabeculae which showed surviving myocardium with hypertrophy, degenerative changes and increased interstitial fibrosis. The free left myocardial wall showed patchy replacement fibrosis and scattered interstitial collections of mononuclear cells. ARVC, as a common cause of sudden death of the young adults, is not enough explored. Under these circumstances, the diagnosis must trigger investigations, not only for disease understanding, but also for preventing unexpected fatal clinical situations.

Key Words: arrhythmia, cardiomyopathy, sudden death

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by gradual replacement of myocytes by adipose and fibrous tissue of the right ventricular wall [1]. Described in 1977 [2], is considered a potentially lethal cause of cardiac disease. This disorder usually involves the right ventricle and has been associated with arrhythmia, heart failure, and sudden death [3]. In this paper, we report a case of a 21-years-old patient who died suddenly after a ventricular arrhythmia related syncope. A morphological autopsy exam was performed with revealing of findings, that support ARVC diagnosis according with task force international group agreement [4, 5], and features corresponding with postmortem hallmark of cardiac arrest.

Case Report

A 21-year-old male, with no history of cardiovascular diseases or previous exercise related cardiac symptoms, was unresponsive at resuscitation CV maneuvers, on March 2011. The patient died during sport activity and anybody was unable to inform on episode syncope duration. There is no history of heart disease or cardiac sudden death between members of the family, as well. At necropsy all the cardiac chambers were grossly enlarged and the heart weight was increased, having around 400g. The coronary arteries were normal. The left ventricular wall was 7 mm thick

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whereas the right ventricular wall was very thin (1 mm) and infiltrated by adipose tissue.

The histology of the free wall of the right ventricle clearly showed transmural fibro-fatty replacement (Figure 1). The pathological process, extending from the subepicardium to the endocardium in a wave-front pattern, presented a lace-like appearance.

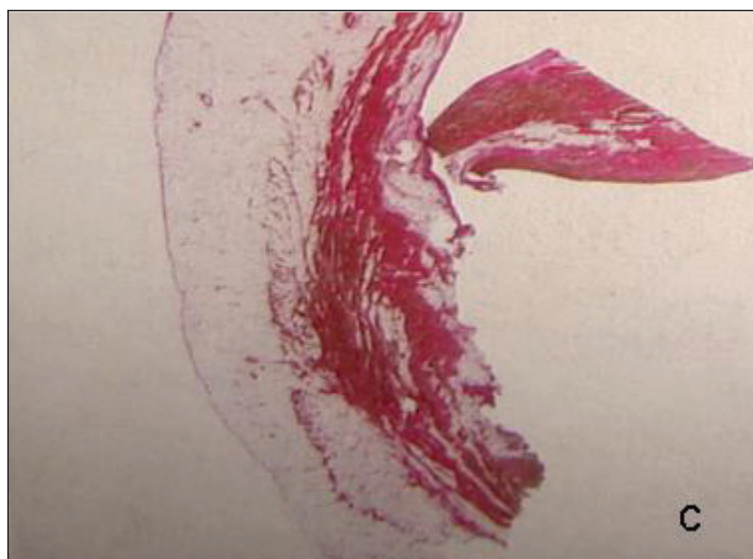
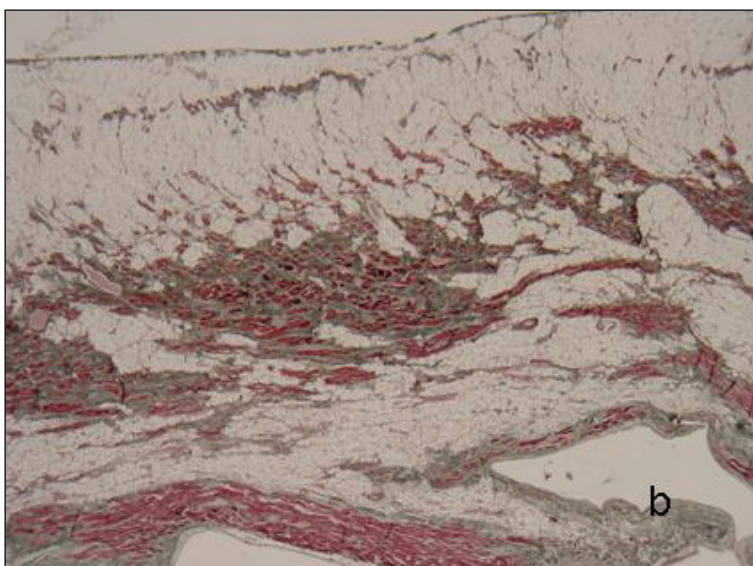
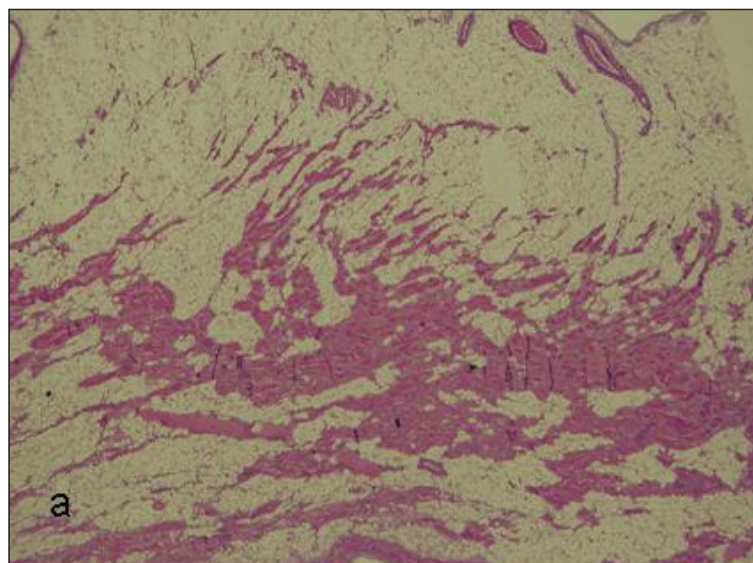


Figure 1. Right ventricular wall with transmural fibro-fatty replacement (a-Hematoxylin-eosin=HE; b-Masson; c-Van Gieson staining;)

At microscopical examination, the remaining cells were either hypertrophied or attenuated (Figure 2a) and presented many other lesions, consisting in wavy cell elongation (Figure 2b), contraction band necrosis (Figure 2c) and focal segmentation of the hypercontracted myofibers (Figure 3), as a substrate of ventricular fibrillation. The tissue samples from left ventricle wall showed a heterogeneous picture with variable degrees of myocardial injury and repair including acute necrosis with inflammatory infiltrates (Figure 2a), subacute damage with active fibrosis and adipocytes replacing myocytes (Figure 3), and chronic damage with mature fibrous tissue and adipocytes surrounding residual surviving myocytes (Figure 2b).

Discussions

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary myocardial disorder, characterized by a high incidence of arrhythmias and sudden cardiac death. It is listed among cardiomyopathies in the recent WHO classification [6] and is defined by transmural fatty or fibro-fatty infiltration of the right ventricle.

Arrhythmogenic cardiomyopathy is a cause of sudden death. In cardiomyopathies, the highest frequency (50%) of sudden death was observed in hypertrophic cardiomyopathy, followed in decreasing order by dilated cardiomyopathy (14%), while sudden death was rarely reported in restrictive cardiomyopathy. In arrhythmogenic cardiomyopathy, a high frequency of sudden death was noted without of percent figure offered [7].

As in this case, Thiene [3] notes that ARVD sudden death is more likely in young adults than in children, and males are more susceptible to that event than females.

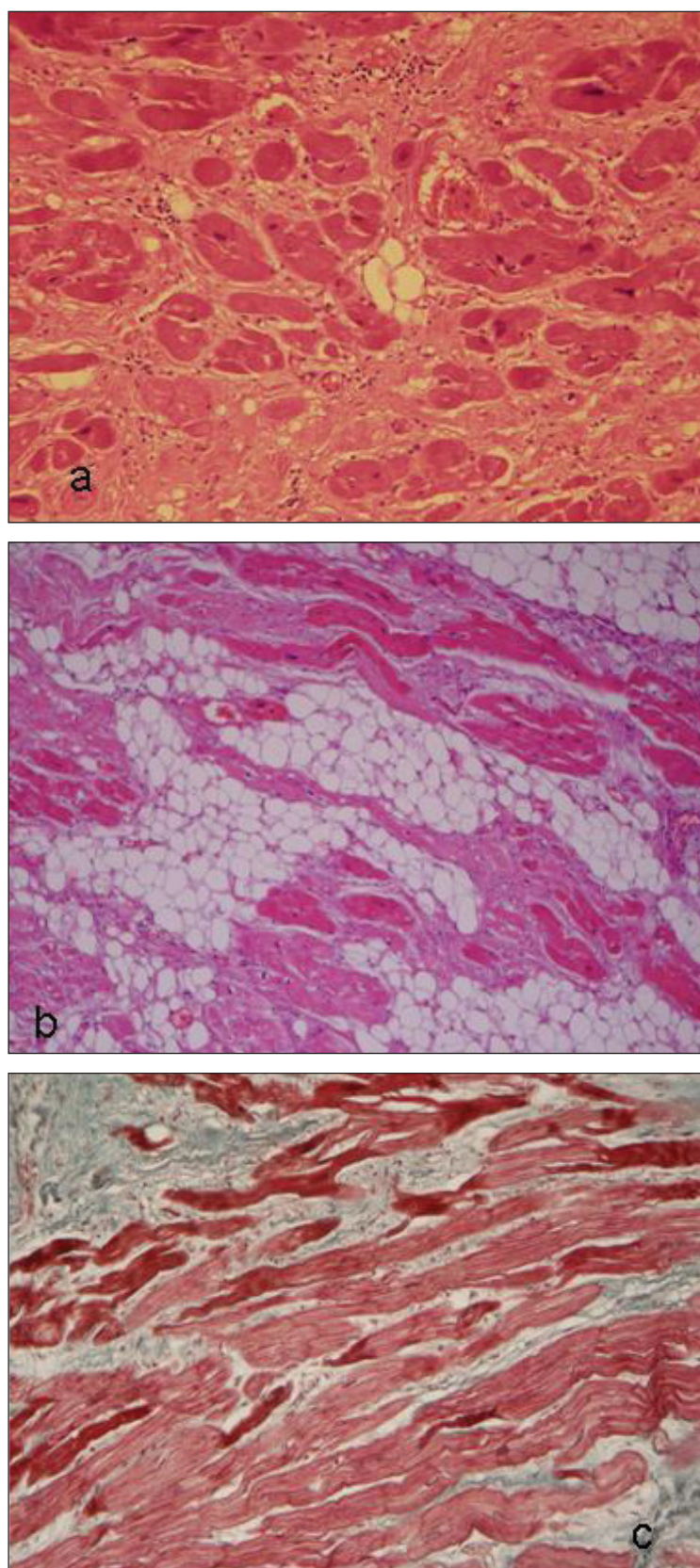


Figure 2. a-Hypertrophied and atrophied cardiomyocytes and inflammatory infiltrate (HE); b-Wavy elongated cardiomyocytes (HE); c-Contraction band necrosis (Masson)

ARVC, because a certain amount of intramyocardial fat is normally present in the right ventricle antero-lateral and apical region even in the normal heart and increases with age and body size. She considers that the presence of replacement-type fibrosis and myocyte degenerative changes are essential to provide a clear-cut diagnosis, besides remarkable fat replacement [11].

It is well known, that arrhythmogenic cardiomyopathy mainly affects the right ventricle, with partial and total atrophy of the myocardium and fatty or fibro-fatty replacement. Corresponding with Thiene observations [3], a phase of active lymphocytic myocarditis apparently precedes myocyte necrosis or apoptosis. In his pathologic studies, Anderson appreciates that about 50% of cases have left ventricle involvement, including adolescents [1]. In this case, we found the involvement of both two ventricles. As in Anderson [1] notes, we consider that the disease progression can lead to diffuse right and left ventricle free wall involvement, but even in advanced disease, the interventricular septum tends to be spared, because of lacking of subepicardial area, as a beginning ARVD focus.

Sudden death in this disease is related to dysrhythmias generated at the junctional regions between atrophic and normal myocardium, hence the name of arrhythmogenic. The disease name reflects the usual predominant involvement of the right ventricle, but increasing recognition of biventricular involvement explains adoption of the broader term of arrhythmogenic cardiomyopathy [8, 9].

In this case, corresponding with Thiene notes, the right ventricle was dilated and its free wall was yellowish and partly translucent. Histologically, the substitution of the right ventricle myocardium with fibro-adipose tissue associated with lymphocytic infiltrates was the ARVD hallmark. The replacement was extended transmurally, except for hypertrophied subendocardial myocytes, findings described by Thiene, as well [10].

Basso observed that fatty infiltration of the RV is not considered “per se” a sufficient morphologic hallmark of

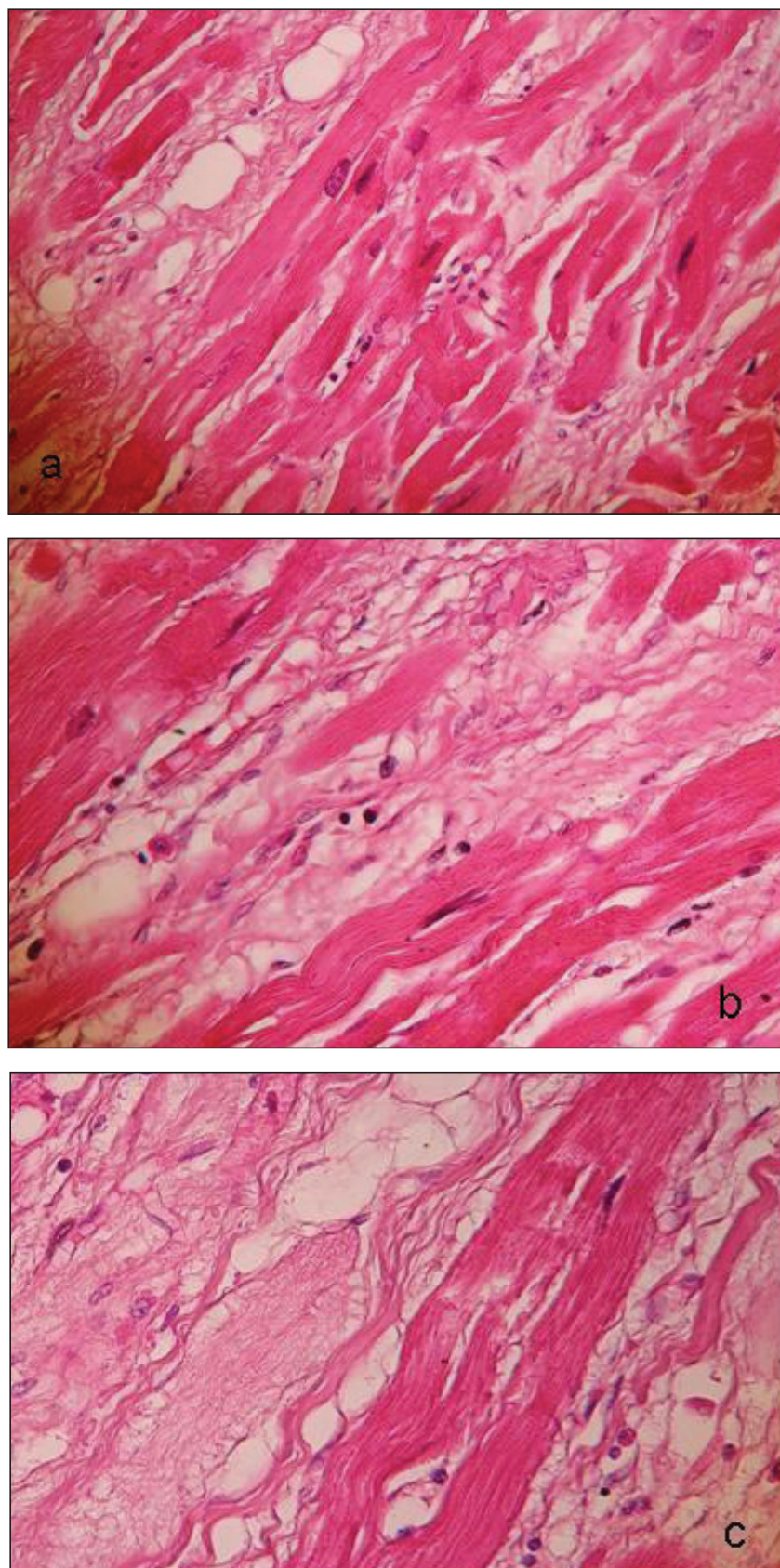


Figure 3. Cardiomyocyte segmentation and contraction band necrosis Hematoxylin-eosin staining-a; b; c;

The severe atrophied right ventricle myocardium replaced by fibro-fatty tissue, in Angelini opinion, should be regarded as a healing phenomenon following myocyte deaths [12]. Indeed, the fibrous tissue presented in variable amounts, is an essential part of the healing process and plays a fundamental role in the intraventricular conduction delay of the electrical impulse, which is at the basis of onset of the life-threatening arrhythmias.

According, with Rossi [13], death of single or multiple myocytes may be associated with inflammatory infiltrates. In some cases, Nava [12] suggested that right ventricular dysplasia may be a consequence of a previous myocarditis. In this case, we have also evidenced mononuclear inflammatory infiltrates in affected areas, but it is unclear whether this is a primary manifestation of disease or develops as a secondary response to myocyte injury. In other scenario, Thiene [14] appreciated that inflammation could play a pathogenic role in tissue injury and arrhythmogenesis, although this potential mechanism remains largely unexplored.

Physiologically, the fibro-fatty replacement of the myocardium interferes with intraventricular conduction of the electrical impulse accounting for electrical impulse delay and onset of re-entrant phenomena which are the mechanisms of ventricular arrhythmias. So, a more extensive quantitative study of myocardial functional lesions in this cardiomyopathy could help in understanding the cause of cardiac arrest at autopsy.

A very important issue is the postmortem recognition of cardiac arrest. It may have relevance from a forensic point of view, in establishing the cause of death. It is known that the heart may stop after ventricular fibrillation, generally preceded by a malignant arrhythmia, or in asystole as an end result of bradycardia, or in electromechanical dissociation, which is, the loss of mechanical function despite a normal electrocardiogram [7].

At present, the morphologic background for different types of cardiac arrest is poorly defined, and apart from a few striking conditions (e.g., heart rupture plus tamponade), we cannot structurally diagnose the cause of a myocardial arrest. Silver studies [15] suggested that different impairments of the contraction-relaxation cycle need a reconsideration of myocardial changes in this fatal, terminal event.

As in this case, the main type of cardiac arrest predominant in sudden death is ventricular fibrillation resulting from arrhythmogenic conditions. The development of ventricular fibrillation is the result of imbalance between factors that enhance electrical synchrony and factors that decrease electrical asynchrony [16]. The questions are whether morphology of the electrocardiographic pattern exists, what causes it, and how it evolves. Nowadays, the segmentation of hypercontracted myofibers, considered in the past artifacts, is recognized as a possible agonal event related to ventricular fibrillation [15]. Silver has suggested, that various lesions may show a correlation between myofiber breakup and the electrocardiographic chaos: (a) bundles of hypercontracted myocells alternating with bundles of hyperdistended myocardial cells; (b) single or groups of hypercontracted myocardial cells disposed in line with hyperdistended ones; (c) intercalated discs between hypercontracted elements being either widened or stretched or segmented.

In this case, we found the segmentation of hypercontracted myofibers, as a focal lesion, in left and right ventricles of the myocardium.

Another question is related by the stimulus for arrhythmogenic ventricular fibrillation. Corrado (17) considers that impairment in myocardial metabolism could precede ventricular fibrillation. In many experiments, ventricular fibrillation was reduced or abolished by beta-blocking agents, suggesting an adrenergic role. Corrado suggests that a single focus of myofibrillar breakup may correspond to an instantaneous ventricular fibrillation, while an extensive lesion may be associated with a relatively long-lasting malignant arrhythmia. We consider that segmentation and related findings seem to be reliable histological patterns for diagnosing of cardiac arrest due to ventricular fibrillation.

Conclusions

Arrhythmogenic cardiomyopathy is a cause of sudden death in the young. It is very often the first manifestation of the disease. The myocardial involvement is more frequently biventricular than isolated in the right ventricle. The diagnosis could be difficult for cardiologists, pathologists and forensic doctors.

It is clear that fibro-fatty tissue replacement may enhance the electrical ventricular vulnerability and cell death and inflammation act as an acute arrhythmic trigger in the setting of the chronic substrate of fibro-fatty replacement. These evidences may open new avenues not only in the understanding of the disease, but also to conceive new diagnostic and therapeutic strategies.

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