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# Arrhythmogenic Right Ventricular Dysplasia – Analysis of Three Fatal Cases

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Arrhythmogenic right ventricular dysplasia (ARVD) is an underrecognized clinical entity, with unknown cause and prevalence and with a frequent familial occurrence. It is characterized by progressive degeneration of cardiomyocytes and fatty replacement of right ventricular cardiomyocytes, which causes electrical instability and sudden death. ARVD is a rare disorder, but for a short time, three cases were proven by autopsies in a small region in Bulgaria. All of them died suddenly without data for preliminary disease. In all cases, the myocardium of the right chamber was partially replaced by adipose tissue. The gross findings resembled an acute myocardial infarction and if no histology of the right chamber is performed, the diagnosis of ARVD may be easily overlooked. Proper diagnosis is important because: (i) an recessive form of ARVD is common in neighboring countries, and (ii) relatives should be informed and followed up for premorbid diagnosis.

*Key words*: sudden death, ARVD, cardiomyopathy, lipomatosis, adipose tissue.

## Introduction

Arrhythmogenic right ventricular dysplasia (ARVD), or cardiomyopathy (ARVC) is an underrecognized clinical entity, with unknown cause and prevalence and with a frequent familial occurrence (1, 2). Morphologically, it is characterized by progressive degeneration of cardiomyocytes and fibro-fatty replacement of right ventricular myocardium, causing electrical instability, ventricular tachyarrhythmias with left bundle branch block and sudden death at a young age (3, 4, 5). ARVD is a rare disorder, but for a short period of time, three cases were proven by forensic pathology autopsies in a relatively small region in the northeastern part of Bulgaria.

The aim of the present study is to analyze the autopsy findings in these cases.

## Results

Case No 1. 26-year-old man, dying suddenly during minor physical effort (No 403/2006, blood group Aβ, no alcohol in blood)

Case No 2. 42-year-old man, found dead in a toilet room at Albena resort (No 104/2007, blood group Aβ, no alcohol in blood)

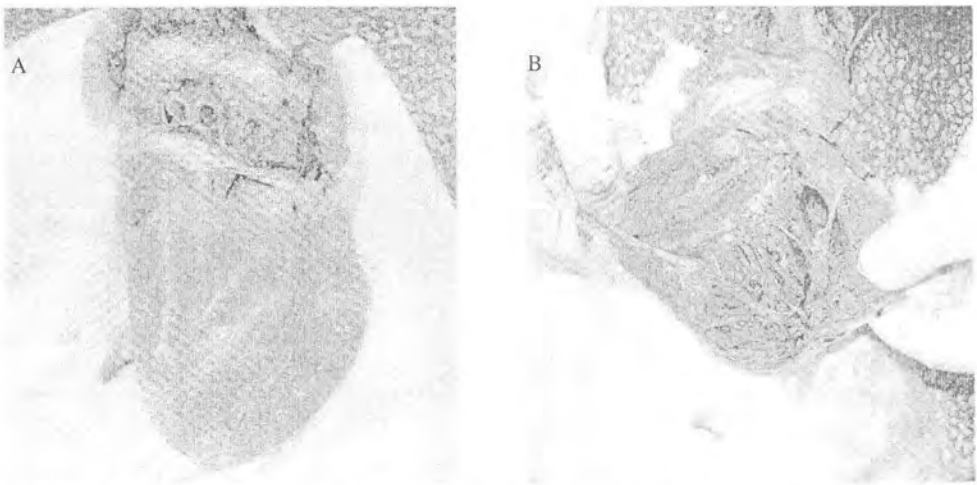


Fig. 1. Case 1, right cardiac chamber, slight dilation (A), spotty endocardial surface (B)

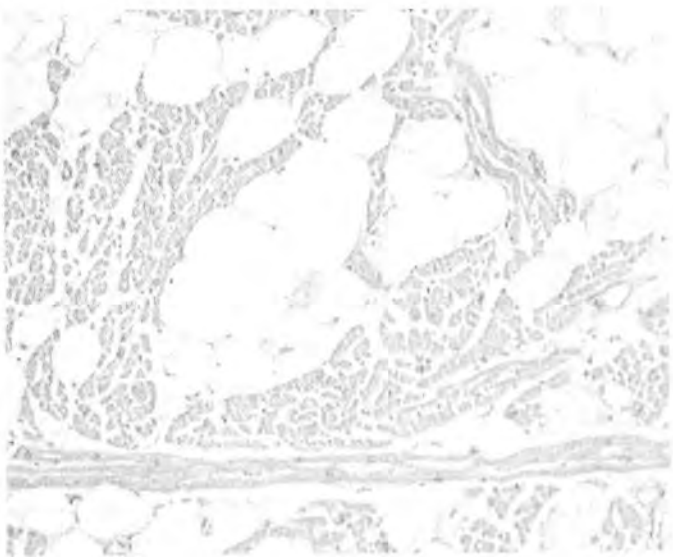

Fig. 2. Case 1, streaks of adipose tissue replace the cardiomyocytes in the right chamber. HE, × 100

Case No 3. 50-year-old woman, dying suddenly in the Outpatient clinic – Balchik (No 132/2007 – blood group Aβ, 0.4‰ alcohol in blood – subclinical level of alcohol affect). In all cases there were no data of previous complaints or disease.

The gross findings in all the three autopsy cases were consistent of signs for rapid occurring death – severe congestion in all viscera, without postmortem blood coagulation, presence of pulmonary and cerebral edema; no other significant lesions were found.

Changes in the hearts were minimal – slightly dilated cardiac chambers (in Case 1 only the right ventriculus was involved – Fig. 1 A), with spotty endocardial surface and somewhat pale and streaky myocardial cut surface (Fig. 1 B). Major arterial blood ves-

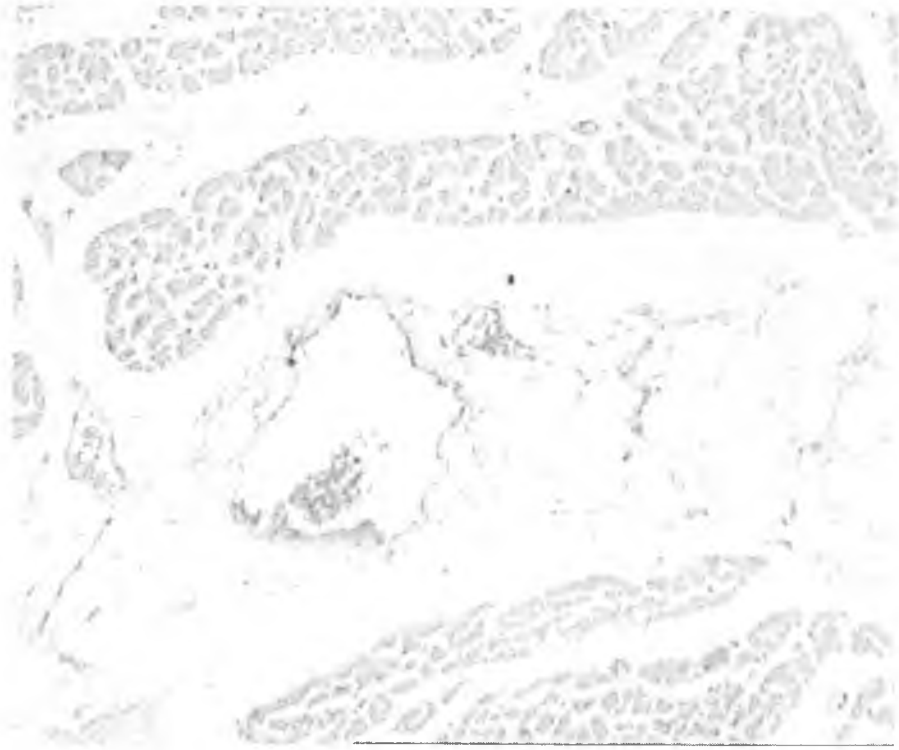

Fig. 3. Case 2, perivascular adipose tissue replacement of the cardiomyocytes in the right chamber. HE, ×100

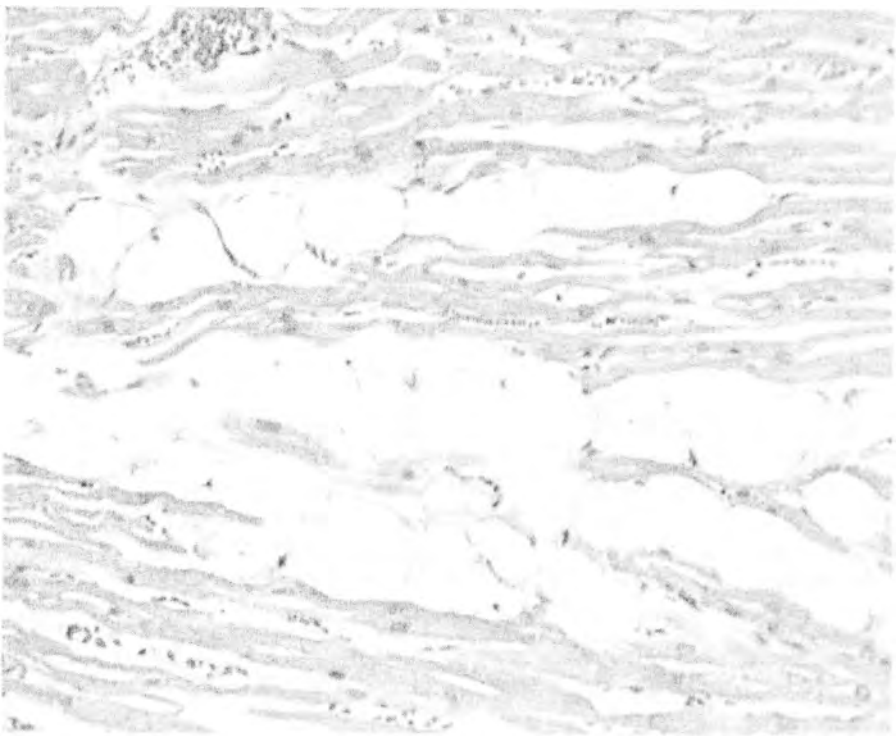

Fig. 4. Case 3, streaks of adipocyte, scattered among the cardiomyocytes in the right chamber. HE, ×100

sels showed minor degree of atherosclerotic involvement: in Case 1 – only in the aorta, in Case 2 and 3 also in the main branches of the coronary arteries without gross evidence of atherosclerotic complications, such as fissures, erosions or thrombosis.

Light microscopy findings in the myocardium of the dilated right heart chambers included increased amount of perivascular adipose tissue forming massive layered fatty infiltrates with signs of degeneration in the surrounding cardiomyocytes (Fig. 2, 3, 4). The myocardium of the left ventriculus appeared normal in Case 1; in Case 2 "wavy" cardiomyocytes were established and in Case 3 the streaks of adipose tissue involved both cardiac chambers.

## Discussion

As fat replacement of cardiomyocytes is the most essential finding in all the three autopsy cases, we consider the gross and light microscopy evidence presented above to be consistent with ARVD. All the cases studied here reveal the typical involvement of the heart without any other significant pathological changes to explain the occurrence of sudden death.

ARVD was first described about 30 years ago [6], while analyzing the causes of fatal ventricular arrytmias. Since then, a considerable progress has been made in the understanding of the clinical presentation, the morbid anatomy and the genetics of ARVD. However, a great lack of information still exists with regard to pathogenesis, premorbid diagnosis, natural history, risk stratification, and prophylaxis of life-threatening complications and prevention of death in patients with ARVD.

It is believed that ARVD is a rare condition, but since the patients usually have no severe complaints and most of them after sudden death are subjected to forensic medicine postmortem expertise, the actual incidence may be considerably higher. It is important to point out, that if no histology of the right ventricular myocardium is performed, ARVD may be easily overlooked. The three cases discussed here were initially diagnosed as suspicious of acute myocardial infarction. ARVD accounts for about 20% of sudden deaths in all individuals younger than 35 years and it was once considered a disease of the young people and athletes [4, 7, 8], but may be diagnosed in the older population [9]. The three cases discussed here belong to both age groups. Therefore, an early and accurate diagnosis followed by appropriate treatment is increasingly important for it may prevent lethal arrhythmias.

In regard to the pathogenesis of ARVD, it is suggested, that an inherited impairment of cell-to-cell adhesion (desmosomal proteins) may be the underlying pathogenic mechanism, via accelerating apoptosis of myocardial cells. Mutations genes encoding desmosomal proteins (Junctional plakoglobin, Desmoplakin, Plakophilin 2, and Desmoglein 2), have been identified in patients with ARVD. It is believed that these primary defects contribute for accelerated apoptosis of cardiomyocytes and secondary fatty or fibrofatty replacement. Since the disorder is inherited, it is of great importance not just to establish the right diagnosis on time, but also to transfer the information to the general practioners, so that genetic studies of relatives and off-springs to be carried out. The recessive form [10] of ARVD, known as Naxos disease (including also features as woolly hair and palmoplantar keratoderma) is more common in regions close to Bulgaria – the Hellenic island and Turkey.

According to the data from the literature [1, 5, 9] histological findings in ARVD may be presented by lipomatosis of the right ventricular myocardium alone, or by combination of lipomatosis/fibrosis. The observations presented here reveal no myocardial fibrosis or admixture of connective tissue alongside with the typical lipomatosis. Some

of the studies report the presence of perivascular lymphocytic infiltration in the zones of adipose tissue infiltrates [12] and consider this feature as important for the development of arrytmia. We did not encounter any lymphocytic infiltrates in our cases.

Another interesting point in the pathogenesis of ARVD is considering the synthetic and secretory activity of adipocytes. Now, it is becoming increasingly evident that adipose tissue is a multifunctional organ that produces and secretes multiple factors (**adipokines**) [13, and their references], that can act in both paracrine and endocrine fashion and thus to induce malfunction of adjacent cardiomyocytes and disturbances of the conduction system.

## Conclusions

The diagnosis of ARVD should be suspected in individuals of all ages who present with a clinical syndrome of sudden death. In all of them, histological investigation of the myocardium of the right chamber should be performed. In case, that ARVD is proved, the information has to be forwarded to the relatives and the medical specialist in concern.

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