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Mixed cardiomyopathy associated with a *DSP* gene variant: a case report and literature review

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A case report of mixed cardiomyopathy (combination of non-compaction cardiomyopathy and arrhythmogenic right ventricular dysplasia) associated with a *DSP* gene variant is presented. The first and only symptom of the disease was sudden cardiac death.

Key words: sudden cardiac death, long QT syndrome, myocardial electrical instability, arrhythmogenic cardiomyopathy, non-compaction cardiomyopathy, genetic variants *DSP* and *KCNH2*.

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Sudden cardiac death (SCD) is one of the leading causes of death in developed countries. SCD in young people is a significant aspect of public health, which incidence (excluding infants) ranges from 0,6 to 6,2 per 100,000 [1]. In the overwhelming majority of cases (85%), the mechanism of SCD is electric myocardial instability, leading to ventricular tachyarrhythmias — ventricular tachycardia and ventricular fibrillation (VF), followed by asystole [2]. According to recent data, the main causes of SCD in people under 35 years of age include arrhythmogenic cardiomyopathy (ACM), channelopathies, hypertrophic cardiomyopathy, left ventricular noncompaction cardiomyopathy (LVNC), coronary artery anomalies and myocarditis [3-5].

According to the 2019 Heart Rhythm Society expert consensus statement, ACM is a hereditary myocardial disease characterized by progressive fibro-fatty replacement of the myocardium involving not only the right ventricle, but also the left ventricle (LV), which can have biventricular forms and clinically manifests as ventricular arrhythmias with a high risk of SCD. Currently, the left ventricular ACM is less studied [5-7].

The prevalence of the disease (depending on the region) is 1:2000-1:5000 [8]. The debut most often falls on the second and third decades of life [6]. According to molecular genetic studies, ACP is most often associated with mutations in genes encoding intercellular junction proteins: desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), plakophyllin-2 (*PKP2*), plakoglobin (*JUP*), desmin (*DES*), and a number of other proteins [9, 10]. The expressiveness and penetrance of clinical and morphological signs in ACM are extremely variable. Factors such as sex, age, physical activity, and chronic intoxication play an important role in the formation of the phenotype [11]. In approximately 3-6% of patients, the cause of disease is the presence of more than one pathogenic or possible pathogenic genetic variant that contributes to the development of the disease phenotype [6]. Patients with ACM associated with the carriage of two or more pathogenic variants, as a rule, have an earlier age of onset and a progressive course, including with a high risk of SCD [6]. At autopsy, 20% of those who die suddenly at the age of 35 years show signs of arrhythmogenic right ventricular dysplasia (ARVD) [12]. In St. Petersburg, according to Gordeeva M. V. et al. (2012), ARVD is a frequent (14,1%) cause of SCD in young people [13].

In the study by Lutokhina Yu.A. et al. (2018) with an average follow-up of 13,5 [4; 34] months, 4 clinical forms of ACM were identified: latent arrhythmic (50%), manifest arrhythmic (20%), ARVD with a with predominant biventricular chronic heart failure (16%) and ARVD in combination with LVNC (14%) [11].

Of interest is the combination of ACM and LVNC, which is also an independent morphological and functional phenotype of LVNC (Table 1).

In the 2006 American Heart Association classification, both ACM and LVNC are defined as primary genetic cardiomyopathies (CM) [4]. The classifications of clinical course of ACMP proposed by Fontaine G in 1995 and 1998 have not found wide practical application for selecyion of management, treatment and prevention of SCD [14, 15]. According to 2008 European Society of Cardiology classification, ACM was identified as a separate type of CM, while LVNC refers to an unclassified CM [5]. At the same time, the separation of mixed morphological and functional phenotypes of CM is the subject of study. This approach is an advantage of the 2013 MOGE(S) classification system [16-18].

The variety of genes associated with non-compaction cardiomyopathy (NCC) suggests its phenotypic heterogeneity. By now, ideas about the genetic basis of myocardial non-compaction have expanded, not only as a concomitant phenotype in genetic CM, but also as a component of other heart diseases — congenital heart defects and some orphan diseases [4, 19]. The phenotype of myocardial non-compaction can be formed under the influence of coexisting multiple genetic variants [20], determined by epigenetic and environmental factors [21].

There are 9 different morphofunctional phenotypes (Table 1) [6].

Differential diagnosis in NCC is in some cases extremely difficult due to its phenotypic heterogeneity.

This article presents a clinical case of SCD in a 21-year-old woman with mixed CMP (NCC+ACM), complicated by VF and myocardial infarction (MI).

Case report

Twenty-one-year-old female patient suddenly lost consciousness. The collection of medical history was carried out with relatives. Before this case, the patient did not seek medical help. Intake of drugs and alcohol was ruled out.

Table 1
Morphofunctional phenotypes of NCC [6]

1. LV non-compaction 2. RV non-compaction 3. Biventricular noncompaction 4. NCC+DCM 5. NCC+HCM 6. NCC+RCM	7. Mixed form: — NCC+HCM+DCM or — NCC+DCM+RCM 8. NCC+CHD 9. NCC+ACM

Abbreviations: ACM — arrhythmogenic cardiomyopathy, CHD — congenital heart disease, HCM — hypertrophic cardiomyopathy, DCM — dilated cardiomyopathy, LV — left ventricle, NCC — non-compaction cardiomyopathy, RV — right ventricle, RCM — restrictive cardiomyopathy.

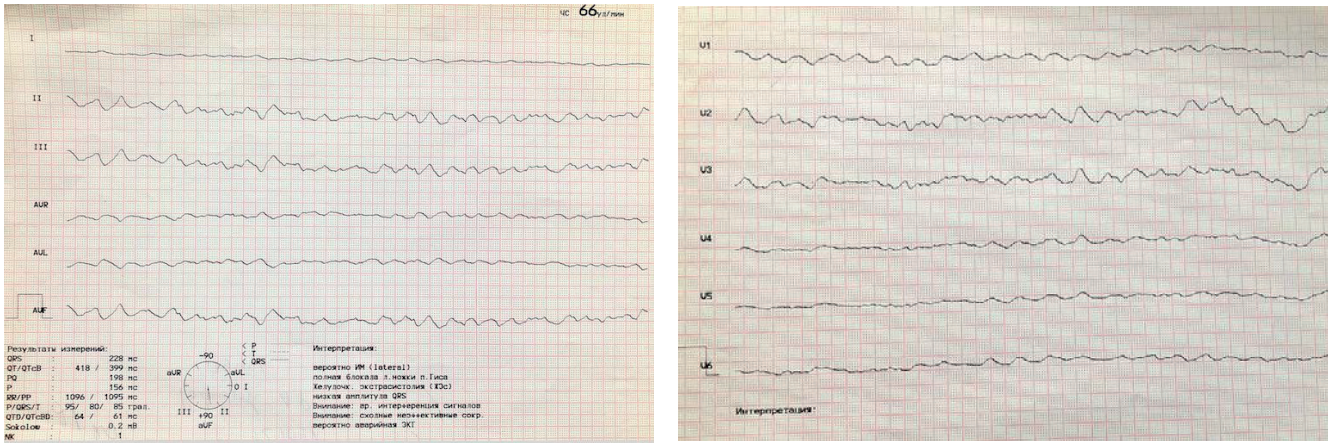

Figure 1. Cardiac arrest (VF). Paper speed: 50 mm/sec.

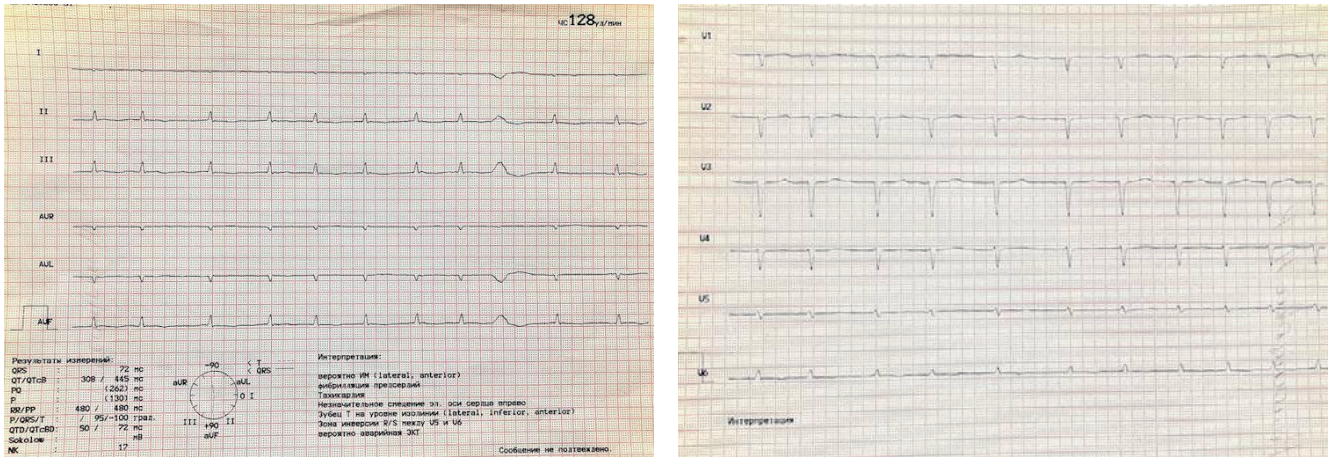

Figure 2. ECG of a 21-year-old female patient with mixed CMP: NCC and arrhythmogenic dysplasia associated with genetic DSP and KCNH2 variants. Paper speed: 50 mm/sec.

Collection of a genealogical history revealed that the father suddenly died at the age of 35 (no medical information).

At the time of ambulance arrival, the patient's condition was very ill — stage II-III coma, areflexia. Spontaneous breathing, central pulse. Blood pressure were not determined. Cardiopulmonary resuscitation was immediately started.

Electrocardiography (ECG) recorded the VF (Figure 1). Defibrillation, intravenous infusion of amiodarone, tracheal intubation and artificial lung ventilation with the Drager Oxylog system was carried out. Lucas II chest compression system was used.

An emergency implantation of an extracorporeal membrane oxygenation (ECMO) system was performed. Against the background of intensive therapy, atrial fibrillation (AF) was recorded with a ventricular rate of 83 bpm (RR, 0,72 sec; QRS, 0,07 sec). Right axis deviation, transition zone between V4 and V5, non-rise of r wave from V1 to V4 (rS). Diffuse repolarization changes presented as weak negative and weak positive T waves. Attention was drawn to the decrease in the QRS voltage (Figure 2).

Cardiac monitoring revealed a transient QT prolongation up to 0,440 sec. According to Bazett's formula, QT_{corr} was 0,518 sec.

Due to technical difficulties (extracorporeal membrane oxygenation), it was not possible to obtain a high-quality image with echocardiography. At the time of admission, there were no significant structural cardiac changes (Figure 3A); increased LV trabecularity was noted (Figure 3B). A repeated examination performed at the end-stage disease showed a significant decrease in global LV contractility (LV ejection fraction, 20%) due to severe hypokinesia, asynchronous LV contraction. The severity of the condition did not allow for cardiac magnetic resonance imaging.

According to laboratory tests, a significant increase in the venous troponin I level (⩾33,9 ng/ml) was revealed [22]. MI was suspected. Coronary angiography (CA) did not reveal any significant pathology.

Pulmonary angiography also did not reveal structural changes. Pulmonary artery pressure was within the normal range (13-15/1-3 mm Hg). According to angiography, carotid, vertebral arteries and their intracranial branches had no abnormalities.

The absence of significant atherosclerotic lesions of epicardial coronary arteries did not rule out the suspected type 2 MI within the unknown CM [23-25].

The severity of the patient's condition was specified by postresuscitation syndrome, an increase in multiple organ failure: hepatic, renal, respiratory, cerebral (anoxic brain damage), Killip IV acute heart failure. Despite the ongoing intensive therapy, after 4 days the patient died without recovering consciousness.

Post-mortem examination

The central changes were found in the cardiovascular system. Other systems and organs were without significant findings.

The heart is cone-shaped with a pointed apex measuring 12,0x10,0x6,5 cm, weighing 220 g; cardiac index — 0,003 (Figure 4A).

Epicardium of uneven thickness with areas of thinning or growth of adipose tissue.

Valvular endocardium. The *mitral valve leaflets* are with myxomatic transformation, dome-shaped bulging into the left atrium, *jelly-like* in consistency, off-white, unevenly thickened with single small nodular thickenings ~3 mm in diameter. Mitral valve leaflets with growths of whitish dense tissue extending to the subvalvular endocardium. Chordal bands are whitish, some of them with local thickening up to 3 mm, some — thinned and elongated. Multiple additional chords are identified: longitudinal, diagonal and transverse, which in some areas create a net structure. The *aortic valve leaflets* are smooth, mobile, unevenly thickened mainly in the area of fibrous ring. In the area of transition to aortic bulb, yellowish non-protruding spots and white-yellow slightly protruding plaques were revealed.

Pulmonary valve leaflets are smooth, shiny, slightly unevenly thickened due to the connective tissue proliferation. The *papillary muscles are enlarged*, with growths of a whitish dense shiny tissue, especially pronounced in the LV. Some papillary muscles have a transverse attachment. In the LV cavity, mainly in the apex, there are additional trabeculae. Abnormal trabeculae are most pronounced in the apical, median-lateral and lower parts of the LV (Figure 4A, 4B). Between the trabeculae of both ventricles, as well as in the right atrial appendage, multiple dense dry gray-red *thrombotic masses are determined, which are difficult to separate from the endocardium* (Figure 4A).

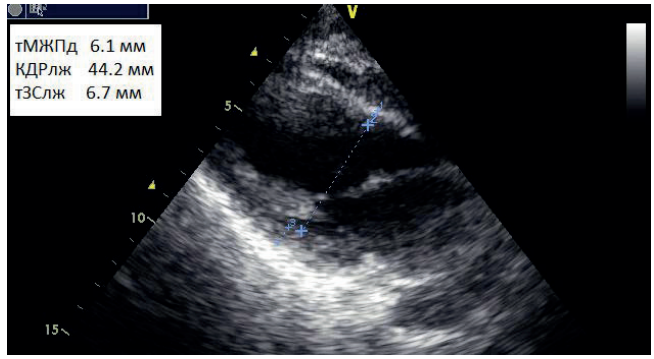

Figure 3A. Echocardiography of a 21-year-old female patient at the time of admission. Parasternal long axis view.
Abbreviations: LV EDD — left ventricular end-diastolic dimension, LVPWT — left ventricular posterior wall thickness, IVSTd — interventricular septal thickness at diastole.

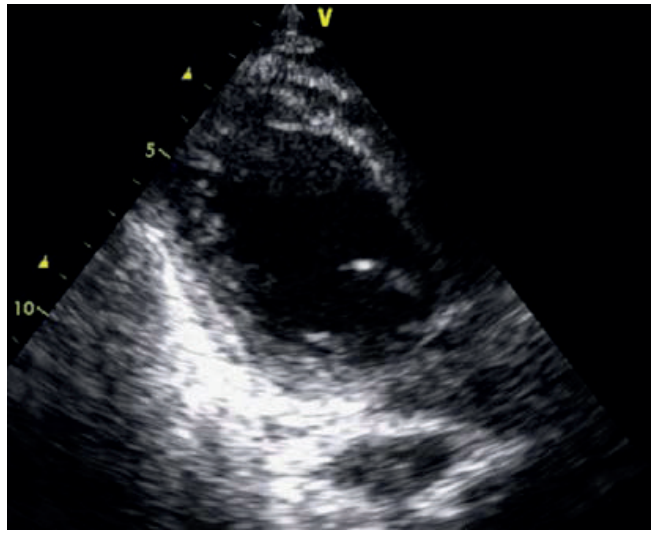

Figure 3B. Echocardiography, apical oblique view. In the area of LV apex and median segments of the inferior wall, there are additional trabeculae.

Red myocardium of a sloppy texture with diffuse growths of a whitish dense tissue and areas of violation of fibrous fine net-like structure. In the area of apex and interventricular septum (IVS), the mottled myocardial tissue with alternating yellowish and dark brown areas. In other areas, the myocardium is flabby with yellowish structureless layers. In the myocardium, the ratio of non-compact to compact layer was 3:1 (Figure 5A, B).

Coronary artery lumen was narrow throughout the entire length (up to 2 mm); the intima was yellow-gray, shiny with single lipid spots.

Right and left coronary arteries is narrowed due to circulated lipid deposits and fibrous plaques, narrowing the lumen of blood vessels by up to 50%. In the intramyocardial vessels, there are signs of acute discirculatory abnormalities and parietal thrombi. *Disorganization of collagen fibers, focal elastolysis, elastofibrosis in the arterial wall.* In the lumen of

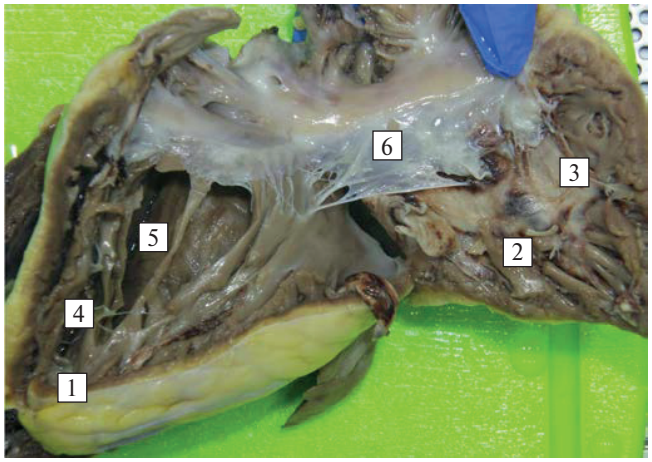

Figure 4A. Gross specimen. Pointed apex (1), subendocardial fibrosis (2), mixed parietal thrombus (3), additional chords (4), increased trabecularity (5). Indistinct structure of valvular endocardium (6).

Figure 4B. Gross specimen. Severe trabecularity and subendocardial motley structure.

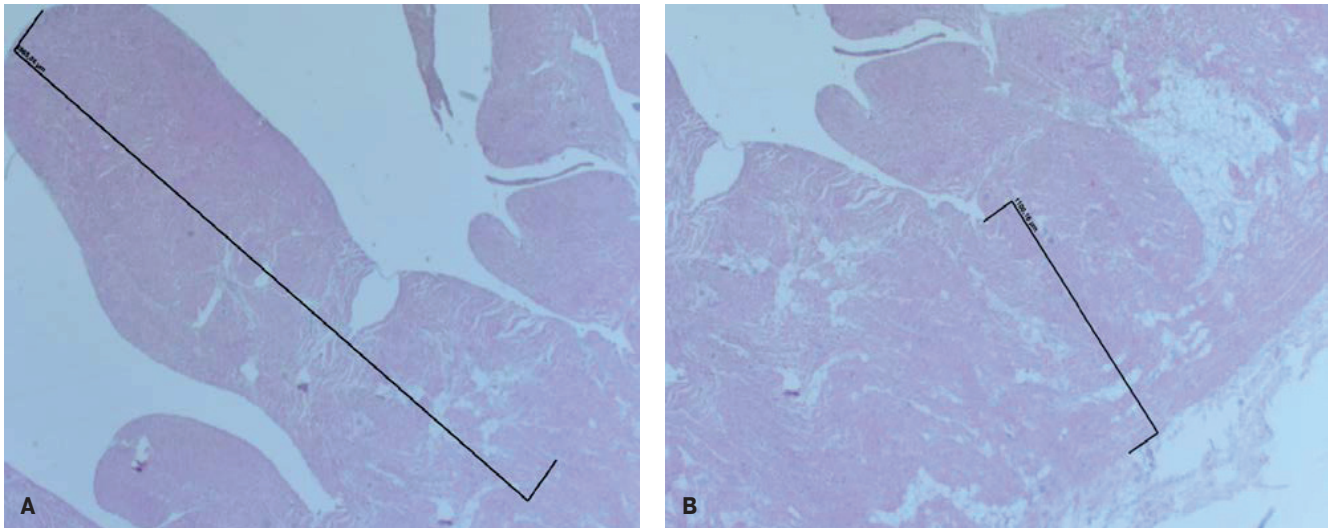

Figure 5A, B. Histological specimen of the myocardium: ratio of non-compact to compact layer, 3:1. Hematoxylin and eosin staining, x100.

small intramural vessels and distal parts of anterior interventricular and circumflex left coronary artery, dark red masses with a rough surface obturating vessels were revealed.

In the area of apex and IVS, myocardial tissue is variegated with alternating yellowish and dark brown areas. On the LV anterior wall with the transition to IVS, merging heterogeneous variegated foci are located. In this area, pale, yellowish, whitish and pink-red areas alternate. In the LV, diffuse and in places merging foci of ischemia and necrosis were found. In the cytogenic stroma with newly formed vessels, single lymphocytic accumulations are determined.

The total area of foci is ~28 cm^2. In the middle third of IVS, a focus of a similar type with an area of 10,5 cm^2 was found. There were areas of undulating deformation, fragmentation, dissociation, myocytolysis of muscle fibers, as well as large fields of fibrosis (Figure 6D).

Microscopic examination revealed changes in the left and right heart. The most pronounced abnormalities were detected in the LV myocardium with fields of rather normal muscle fibers and areas with lipomatosis, focal fibrosis, angiomatosis, among which there were groups of cardiomyocytes with polymorphic nuclei, foci of fragmentation and myocytolysis, areas of stromal basophilia (Figure 6A, 6C). In the right ventricle (RV), growths of adipose tissue were revealed. The residual area of cardiomyocytes in the RV in 1 sample was ~70%. The proportion of adipose tissue was 3%, and fibrous tissue — ~40%.

In the parietal and valvular endocardium, there were signs of connective tissue disorganization with a

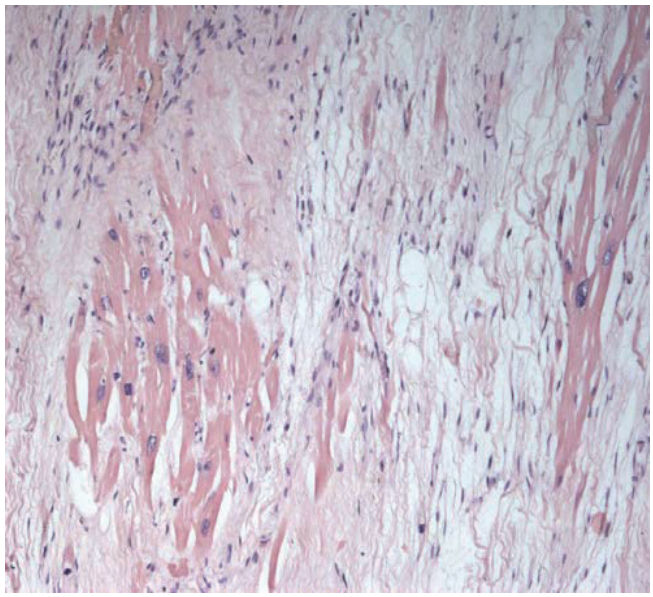

Figure 6A. LV myocardium: focal and interstitial fibrosis, angiomatosis and cardiomyocyte fields with polymorphic nuclei, foci of fragmentation and myocytolysis. Hematoxylin and eosin staining, x240.

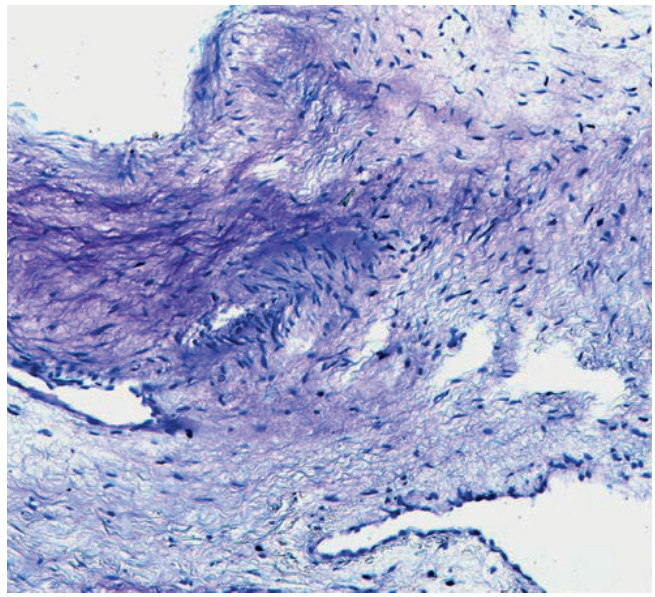

Figure 6B. Mitral valve: myxomatosis and superficial disorganization of connective tissue (mucoid swelling). Toluidine blue staining, x200.

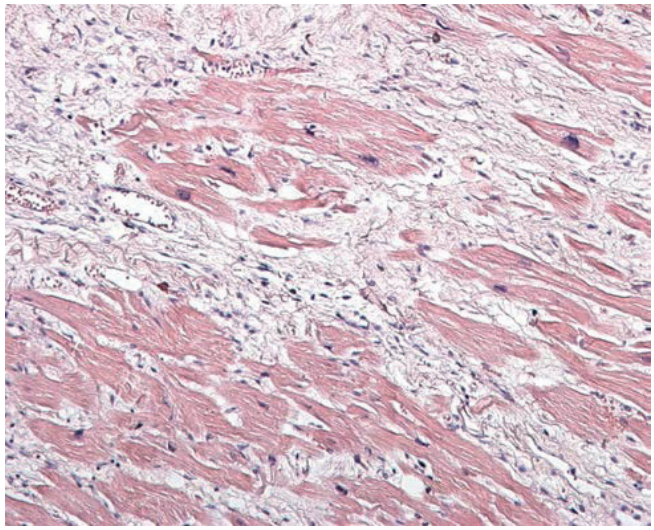

Figure 6C. LV myocardium: foci of the cellular stroma with basophilia. Hematoxylin and eosin staining, x240.

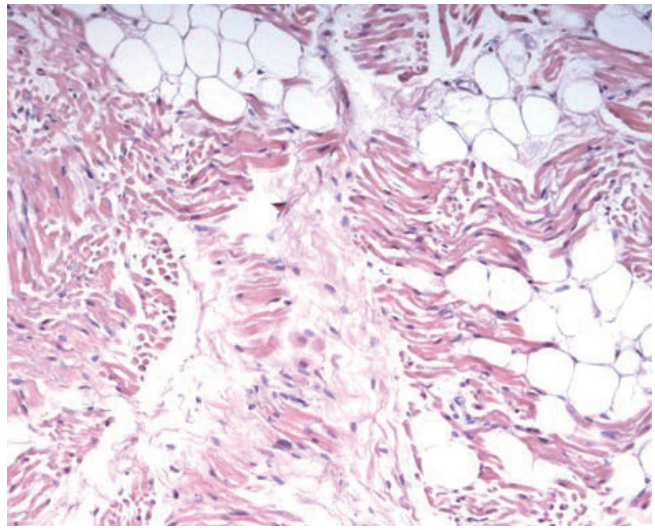

Figure 6D. RV myocardium: focal lipomatosis and undulating deformity of cardiomyocytes. Hematoxylin and eosin staining, x240.

predominance of mucoid swelling; in the heart valves, focal myxomatosis of varying severity was observed (Figure 6B). Growths of fibrous tissue were also found in the RV endocardium. In the myocardial stroma there were single (1-3) lymphocytes (Figure 6D).

Genetic analysis

To clarify the genetic nature of disease, a postmortem genetic testing was carried out using a new generation sequencing and Sanger sequencing with an Illumina MiSeq system.

A mutation in the *DSP* gene was found (uc021yle.1:exon23:c.C3300G:p.C1100W), which, according to the 2015 American College of Medical Genetics and Genomics (ACMG) classification, is with uncertain significance, however, taking into account the clinical performance can be causal [26].

A variant in the *KCNH2* gene (uc003wic.3:exon13:c.C3133T:p.L1045F) was also found, which, in accordance with the ClinVar database and ACMG classification, is considered as benign [26].

Thus, in young women:

- cardiac arrest was diagnosed against the background of electrical myocardial instability (VF);
- AF and long QT syndrome have been reported after cardiac arrest due to VF;

• echocardiography revealed additional trabeculae in the area of LV apex and inferior wall median segments;
• family history of SCD in two generations (unexplained death of the father under the age of 35 years);
• pathological examination revealed:
— hypertrabecularity/LV non-compaction;
— decrease in the cardiomyocyte area mainly in the RV myocardium, myocytolysis, foci of fibrosis and lipomatosis;
— parietal intracardiac blood clots; thrombi in intramyocardial vessels;
— coronary system anomalies;
— recurrent MI of various ages.

Discussion

Based on the comparison of macro- and microscopic abnormalities, it can be stated that the patient had NCC [27].

The clinical and morphological performance in this case also meets the criteria for ACM [6]. The initial morphological manifestations of ACM identified in the RV could also contribute to electrical cardiac instability and SCD.

Both ACM and NCC can manifest as symptoms and/or documented AF, conduction disorders, and tachyarrhythmias of RV and/or LV origin [28]. Repolarization abnormalities, recorded in patients with LVNC and in patients with ACM, also predispose to malignant ventricular tachyarrhythmias and SCD [27, 29]. The most typical repolarization disorders in this pathology are early repolarization (~40%) and long QT syndrome (50%) [30-32].

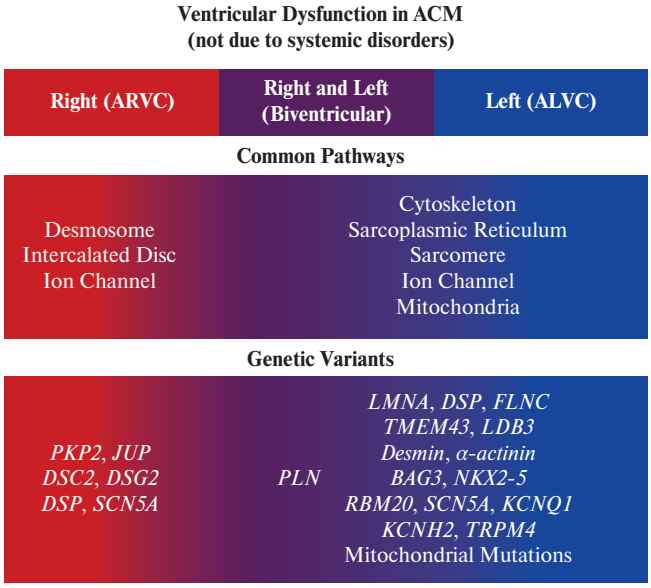

Figure 7. Approach to understanding the common pathway and genetic variants in a patient with arrhythmogenic cardiomyopathy (ACM) according to the predominant ventricular dysfunction [6]. **Abbreviations:** ALVC — arrhythmogenic left ventricular cardiomyopathy, ARVC — arrhythmogenic right ventricular cardiomyopathy.

The classic triad of *LVNC* complications includes: arrhythmias, including SCD, heart failure, systemic embolism. The disease can be asymptomatic for a long time [33-37].

The presence of intracardiac blood clots described in the patient may be an independent manifestation of NCC. Thromboembolic events occur in 5-38% of cases of LVNC [38]. It is extremely rare for NCC and the associated primary antiphospholipid syndrome, which in this case cannot be confirmed or ruled out [39, 40].

MI was clinically suspected (venous troponin I level 33,900 and than >50,000) and was confirmed by postmortem analysis. The literature describes combination of LVNC and subacute or acute type 1 MI of atherogenic origin in patients over 45 years of age [41-45].

Güvenç TS, et al. (2012) report a case of embolic MI in intact coronary arteries according to CA data in a 20-year-old man with LVMN [46]. Pulignano G, et al. Also described embolic MI in a 67-year-old woman with LVNC and LV thrombus. (2015) [47]. Despite this, the association of LVNC with coronary artery disease and MI is rare [48]. In this case, on the one hand, there is an abnormal structure of coronary system (narrow coronary arteries), which contributes to myocardial ischemia. On the other hand, the lumen of right and left coronary arteries was narrowed by up to 50% due to circular lipid spots and fibrous plaques. It cannot be ruled out that this fact may have clinical and hemodynamic significance.

Thus, LV lesions in this case are the result of a combination of non-coronary and coronary mechanisms. At the same time, this is, first of all, the result of chronic and acute dyscirculatory disorders in the intramyocardial arteries with creation of thrombi and thromboemboli.

Desmoplakin is a key element of desmosomes in cardiac and epithelial tissues, which plays the role of a structural component providing mechanical integrity and participates in a number of intracellular signaling pathways [49]. According to reviews, the association of *DSP* gene mutations and LVNC has been described by a number of authors [50-54]. Li S, et al. (2018) found that the development of LVNC among Chinese patients (n=100) is most often associated with the *TTN*, *MYH7, MYBPC3*, and *DSP* genes. The authors also emphasize that patients with LVNC and *DSP* genetic variants have a high risk of ventricular arrhythmias [55]. In the review by Arbustini E, et al. (2016), the *DSP* mutation is considered, manifesting as LVNC, LVNC and dilated CM, LVNC and asymptotic left ventricular dysfunction [50].

A current systemic analysis of genetic variants in ACM is presented in Towbin JA, et al. (2019) study (Figure 7) [6]. In 80% of cases of confirmed ACM, there are mutations in the genes of *PKP2, DSP*, and

DSG2 [56, 57]. Left-dominant ACM is associated with defects in *DSP* gene, as well as *KCNH2* and many other genes (Figure 7) [6, 58].

In our case, the described genetic variants may indicate not only the universal role of the structure of intercalated disk and desmosomes in CM origin, but also the existence of an unknown link that "directs" the CM to one or another morphofunctional phenotype [21].

Conclusion

The presented case report once again demonstrates that, regardless of the unique mechanism in embryonic heart development, the genetic spectrum of LVNC significantly overlaps with the other CMs and includes sarcomeric and structural genes, ion channel genes, and genes of intracellular metabolic pathways. Regardless of genetic nature of the disease, a family history of sudden death requires increased attention of clinicians to members of the proband's family for the early diagnosis of CM and prevention of SCD.

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