Sudden death associated with borderline Hypertrophic Cardiomyopathy and multiple coronary anomalies. Case report and literature review.

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Abstract: We report a case of sudden death in a 20 years old male who collapsed just minutes after the beginning of a football training session. The autopsy evidenced the presence of a unique combination of coronary abnormalities: myocardial bridging at the level of both branches of the LCA; abnormal origin of the right coronary artery: 1 mm above the left semilunar valve of aorta; the initial segment of the RCA coursing within the aortic wall (0,7 cm); myocardial bridging at the level of LCX; sinoatrial node artery originated from the LCX. Histological examination revealed the presence of Hypertrophic Cardiomyopathy markers within the left ventricle and interventricular septum and the cumulative effects of the coronary cardiac anomalies on the myocardial blood flow: extensive interstitial and perivascular sclerolipomatosis, dissecting fibrosis at the level of the sinoatrial node, subendocardial hyaline fibrosis.

Key words: circumflex coronary bridging, hypertrophic cardiomyopathy, sinus node fibrosis, anomalous origin of right coronary artery

A 20 years old male, collapsed just several minutes after the beginning of a football training session. The resuscitation attempts were unsuccessful. He was recently transferred to a first league football team, and was considered a promising goalkeeper. The medical check-up, performed immediately after his transfer had not revealed any health problems.

The autopsy evidenced several cardiac abnormal findings. The ostium of the right coronary artery (RCA) was identified above the left aortic sinus and the initial segment of the RCA coursed for 0.7 cm intramurally (fig. 3, 4), within the aortic wall, behind the pulmonary trunk (PT), before leaving the ascending aorta (AA) at the level of the right aortic sinus and finally resuming its normal position within the atrioventricular groove. RCA didn’t give any branches until the posterior interventricular groove where, terminally, was divided in two branches: a short and threadlike one in the interventricular groove, and one which crossed over the left ventricle, after which it ended up in two short and threadlike branches on the diafragmatic face of the left ventricle.

The main trunk of the left coronary artery (LCA) was 1 cm. long and coursed in the left part of the coronary groove, between the PT and the left atrial appendage (LAA); it was then divided into the anterior interventricular artery or left anterior descendent artery (LAD) and the circumflex artery (LCX). The initial segment of the LAD had a subepicardial trajectory within the anterior interventricular groove where the first diagonal branch of the left ventricle (LV) originated; in its course it went under two consecutive myocardial bridges, of 1.68 and, 2.22 cm respectively (fig. 1).
In that course, the LAD further sent off diagonal branches of the LV that passed over the anterior interventricular vein located subepicardially on the left side of the LAD to distribute in the LV anterior wall.

The circumflex artery was thin and short, coursed in the posterior coronary groove beneath a myocardial bridge and ended abruptly in 2 short terminal, descending branches on the pulmonary aspect of the left ventricle.

The first segment coursed in the left coronary groove, inferior to the LAA. From the first 2 mm of LCX, emerged an atrial branch that passed subepicardially beneath the LAA base where it sent off an atrial branch of the LAA; further, that atrial branch of the LCX entered the myocardium of the left atrium (LA) and coursed subendocardially at the level of the superior border of the LA, over the interatrial septum and subendocardially in the superior wall of the right atrium (RA), to distribute in the sinus node area (fig. 2, 3). So, it proved to be a left sinus node artery (SNA).

Summing up, the studied cardiac specimen presented a unique combination of topographical and morphological anomalies:

1. myocardial bridging at the level of both branches of the LCA, more extensive at the level of the LAD;
2. an abnormal origin of the right coronary artery: 1 mm above the left semilunar valve of aorta; an initial segment of the RCA coursing intramurally (0,7 cm) within the aortic wall;
3. myocardial bridging at the level of LCX
4. sinoatrial node artery originated from the LCX.

Besides a discrete uneven thickening of the free borders of the mitral valve cusps, no other gross anatomical abnormalities were noticed (cardiac diameters 11/10/6,5 cm, average thickness of left ventricular wall: 2 cm, septum: 2 cm, right ventricle 0,4 cm). On serial sections differences in colour and texture were detected (pale grey-yellow areas with a fibrous yellow striae) particularly in the lower part of the interventricular septum, left ventricle papillary muscles and in the anterolateral area of the left ventricle (particular at subendocardial level).

**Histopathology investigation**

**Material and methods**

Specimens of proximal aorta, coronary arteries and myocardial tissue from different areas of the anterior wall of the left ventricle, interventricular septum, sino-atrial and atrio-ventricular nodes were taken for histopathology investigation. The selected tissue samples were formalin-fixed and paraffin-embedded. Sections were cut at 5 microns and stained using the standard H&E stain and van Gieson; special stains such as Weigert and Gomory silver stain have also been carried out.

To ensure the reliability of the experimental study, internal quality control of histopathological techniques was performed as a part of an implemented and certified quality assurance system (ISO 9001/2001).

All slides were examined and photographed on a Zeiss AxioImager microscope. Digital images acquired with Zeiss Axio Vision program have been processed and analyzed with ACDSee Pro Photo Manager 3.0, running under Windows XP Professional.
**Fig. 2** The diaphragmatic surface of the left heart. 1. left auricle; 2. left atrium; 3. left ventricle; 4. great cardiac vein. The circumflex artery (arrows) sends off a large left ventricular branch and further courses in the coronary groove beneath a myocardial bridge (*).

**Fig. 3** Superior, anterior and lateral view of the first segment of the left coronary groove and anterior atrial walls. 1. aorta; 2. pulmonary trunk; 3. left auricle; 4. left coronary artery (1.41 cm. length); 5. circumflex artery; 6. anterior interventricular artery; 7. left atria. The specimen presented a left sinus node artery (arrows) that sent off a left anterior atrial branch (*) and further continued subendocardially, beneath the endocardium of the left and right atria. Also, the initial segment of the right coronary artery coursed intramurally, within the aortic wall (arrowheads).
Results
The microscopic assessment of serial sections of the interventricular septum have revealed many areas with focal hypertrophy of myocardial fibres, sometime arranged in short whorls with mild fibrosis (fig. 5). Gomori silver stain has revealed a variable amount of interstitial reticulin fibres (fig. 6).

Unusual for this age was a subendocardial hyaline sclerosis and mild lipomatosis (fig. 7). This lesion was accompanied by a moderate myxoid degeneration of the leaflets at the insertion level.

In the left ventricle was observed an extensive interstitial and perivascular sclero-lipomatosis, with areas of myocardial replacement and focal disarrangement of the cardiomyocytes, (fig. 8), combined with focal moderate hypertrophy of myocytes.
Fig. 6 Variable amount of reticulin fibers between cardiomyocytes, Gomory silver stain, 10x

Fig. 7 Band of hyaline sclerosis (left) and interstitial lipomatosis (right), beneath the endocardium, VG, 5x, 10x
The sino-atrial area has shown nodal cells surrounded by bands of dense fibrous connective tissue, while the atrio-ventricular area has displayed nests of nodal cells with no pathological changes. The histological investigation of the vessels showed a coronary bridging, benign focal intimal hyperplasia in isolated coronary branches and an aortic wall with scattered subintimal “foamy cells” and a few lymphocytes. The lung showed pulmonary congestion and focal edema. No pathology was recorded in liver or kidney.

Discussions

Various studies showed that most sudden deaths in athletes are due to cardiovascular diseases [1-2]; whilst athletes aged over 35 have atherosclerosis as the main cause [2], in younger athletes congenital/genetic diseases [3] and drugs abuse [4] are the most frequent. A prospective study made by Corrado et co.[3] on 33735 young athletes found the main congenital causes of sudden death in athletes less than 35 years old to be: Arrhythmogenic Right Ventricular Dysplasia (ARVD), anomalous origin of coronary artery(ies), diseases of conduction system, mitral-valve prolapse, Hypertrophic Cardiomyopathy (HCM), and myocardial bridging (in this order). Shirley and Adirim, on the other side, through an extensive review of scientific literature found out that about 40-50% of all sudden cardiac deaths in young athletes are due to HCM, with anomalous origin of coronary arteries taking the second place [5].

According to ECS Guidelines the diagnosis of HCM is usually made by demonstrating left ventricular hypertrophy (LVH) associated with a non-dilated and hyper-dynamic chamber, in the absence of any other cardiac or systemic diseases capable of producing that hypertrophy, and independent of whether or not left ventricular outflow obstruction is present [6]. From HCM definition therefore are taken out any secondary forms of hypertrophic cardiomyopathies and also any other types of genetic diseases which can associate left ventricular hypertrophy, like Noonan syndrome, mitochondrial myopathies (Kearns-Sayre syndrome), carnitine deficiency, Hunter’s disease, Friedreich’s ataxia, neurofibromatosis, Hurler’s syndrome, etc [7]. HCM is usually caused by
mutations affecting sarcomeric proteins (beta-myosin heavy chain, myosin-binding protein, troponins I and T, titin, alpha-actinin, alpha-miosin heavy chain, LIM, alpha-tropomysin, etc.) although some non-sarcomeric mutations were recently found to be involved (e.g. mutations in the 7-2-regulatory subunit of the AMP-activated protein kinase, lysosome-associated membrane protein 2, etc.)

Although genetic classifications of cardiomyopathies are considered as standard by both ECS and AHA guidelines [6-7] in clinical practice the old, morphological variants are still widely used. The most frequent form is the asymmetric pattern that affects the interventricular septum more than the postero-lateral segments of the left ventricle [8]. Less frequent are the diffuse form, with concentric ventricular wall thickening, apical pattern (more frequent in Japan), etc.

Natural history of the hypertrophic cardiomyopathy, either asymmetric or diffuse, is extremely heterogeneous. Many patients remain asymptomatic throughout life, some develop severe symptoms of heart failure, and others die suddenly, often in the absence of previous symptoms and at a young age. Therefore, identification of the patients at high risk of sudden death represents a major clinical problem [9].

Usually clinical diagnosis of HCM is not possible until adolescence [10] - although a few newborn cases were cited [11] – when wall thickening dynamics becomes preeminent; classically, if LVH was not quantifiable until 17-18 years old, in adulthood normal to LVH conversion was considered to be an extremely rare event unless a secondary cause determined it [12]; recent studies however shifted this paradigm as new HCM phenotypes were found to be developing in adult life, phenotypes usually associated with silent mutant gene carriers, incomplete penetrance, or age related penetrance [13]. Usually, in order to clinically diagnose HCM a maximal wall thickness of 15 mm or more is required; however, recent studies revealed that any wall thickness can be associated with the presence of HCM mutant genes [6]; HCM with normal wall thickness associates typical histological signs and has an increased risk for sudden death when compared to normal population.

The later is especially important in athletes where borderline maximal wall thickness values (13-14 mm) can be misdiagnosed as athlete’s heart. Cardiac biopsy can in these cases differentiate between this two conditions - the hallmark of CMH is the presence of an bizarre pathological pattern with malaligned cardiomyocytes and extensive fibrosis, with the highest extensions in areas of macroscopical wall thickening [14].

The best age for clinically screening high risk patients for HCM is before 20 years old, as until then HCM becomes easily identifiable by using a multitude of imaging methods (echocardiography, angiography, ECG, MRI). Commonly, sudden death due to HCM appears in the 12-35 years old interval [12]; therefore, in order to diagnose high risk patients (including athletes) before LVH becomes preeminent or in atypical HCM forms with normal/borderline wall thickness a number of genetic screening tests have been developed and used in clinical practice.[13].

If during the autopsy HCM is suspected genetic testing should be mandatory as the family members have a high chance of carrying the mutant gene. Moreover, the family members should be genetically tested even in the presence of normal/borderline maximal wall thickness values as recent studies reveal their potential to develop into HCM at practically any age [13] and the increased risk of sudden death which can appear even before HCM is clinically manifest [15-16].

The implantable cardioverter-defibrillator, which intervenes appropriately to terminate ventricular tachycardia / fibrillation has recently proved to be a safe and effective therapeutic intervention in patients with HCM, both for the primary and secondary prevention of sudden death [17]. Also, it was shown that septal myectomy relieves cardiac symptoms in adults and children with obstructive hypertrophic cardiomyopathy and concomitant mitral valve repair for myxomatous disease requires minor modifications when performed in conjunction with septal myectomy [18].

The second cause of sudden cardiac death in young adults is considered to be the anomalous origin of coronary arteries [5]. Anomalous origin of LCA from the right (anterior) sinus of Valsalva with the LCA passing in between the aorta and pulmonary trunk is the most common variation [5, 19-21]. In a more extensive study conducted by Basso et co.[22] on 27 hearts from athletes who died suddenly and had anomalous origin of coronary arteries, 23 had abnormal origin of LCA and only four
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on of the RCA. Also, by reexamining six hearts they found an intramural course within the aortic wall for three coronary arteries (two left and one right). For each of the six abovementioned cases the supplied myocardium showed signs of acute ischemia (contraction band necrosis, neutrophilic infiltrate, wavy fibers); in three chronic myocardial ischemic damage with patchy replacement-type fibrosis was diagnosed [22]. A study conducted by Taylor et co.[23] on 52 patients with anomalous right coronary artery originating from the left sinus of Valsalva found 13 sudden deaths; most of them were previously asymptomatic and only six were associated with increased physical activity.

MB is usually identified on the left ventricle (LCA, LAD, sometimes diagonal arteries), RCA [24-28] and LCX [28-31] variation being cited less frequently. For example Chen, Wu et co[28], in an angiographic study found the following frequencies LAD – 76.7%, RCA – 10%, LCX – 6.7%, others – 6.6%. MB incidence in the general population is about 1-3%; in patients with HCM the incidence is up to 30% [32-33]. Although myocardial bridging further reduces systolic blood flow, supplementary to the reduction associated with HCM the association of HCM and MB does not determine a statistically significant increase in mortality as regarded to HCM without MB, according to a study conducted by Sorajja et co. on 425 patients with HCM of which had concomitant 64 MB [34].

Our case had a unique combination of morphological abnormalities: borderline LVH with histological appearance of HCM, anomalous origin of the right coronary artery from the left sinus of Valsalva, a proximal course of RCA within the aortic wall, an anatomical variant of LCX artery and LCX myocardial bridging. To our knowledge this is the first published case with this combination. Histological examination revealed HCM markers within the left ventricle and interventricular septum and a high degree of fibrosis within the sinus node. All these anomalies concurred to alter the cardiac electrical conductivity in our case as follows:

- Anomalous origin of the RCA; our case has both abnormal origin (from the left sinus of Valsalva) and a high position of origin. A high position of origin for coronary arteries is associated with increased risk of sudden cardiac death during physical activities [35], especially in hearts with right dominance [36]. Anomalous origin of RCA from the left sinus of Valsalva is also associated with an increased risk of sudden death [37], also probably associated with increased electrical instability due to hypoxia.
- Abnormal course of proximal RCA within the aortic wall. During systole RCA’s lumen is compressed, resulting in a supplementary decrease of the blood flow.
- Myocardial bridging. Even though the association of MB and HCM is not associated with an increased risk of sudden death it does associated a reduction of the blood flow with subsequent hypoxia and electrical instability.
- HCM increases electrical instability due to associated morphological abnormalities like disorganized cellular architecture, myocardial ischemia with subsequent fibrosis, increased interstitial collagen deposits [38], etc., and also functional abnormalities (cardiac output obstruction, decrease of total coronary lumen on myocardial mass ratio, etc.) [39]
- Long, intramyocardial course and abnormal origin of the sinus node artery associated with LCX bridging. This combination of morphological anomalies led to a chronic hypoperfusion of the sino-atrial node, subsequent extensive intranodal fibrosis and electrical instability.

The electrical instability determined by these anomalies was augmented by increased physical activity which finally resulted in the development of a malignant arrhythmia leading to sudden death.

In athletes a basic cardiovascular examination is often not enough to predict the risk of sudden cardiac death; many cardiac or coronary abnormalities are requiring high resolution imaging techniques (coronarography, MRI, angioMRI) or genetic testing in order to be correctly diagnosed.

Even though anomalies such as presented in this article (HCM with borderline maximal wall thickness, myocardial bridging, anomalous origin of coronary artery) are rare in the general population and probably entire population screening is not cost efficient, for athletes these studies should be mandatory as they have a few additional risk factors (sustained exercise tachycardia, athlete’s heart,
sometimes the use of anabolic substances) which can significantly increase the risk for sudden cardiac death.

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Abbreviations

- AA – ascending aorta
- LAD – anterior interventricular artery
- LAD – left anterior descendent
- LCX – circumflex artery
- LA – left atrium
- LAA – left atrial appendage
- LCA – left coronary artery
- LV – left ventricle
- PT – pulmonary trunk
- RA – right atrium
- RCA – right coronary artery
- SCV – superior caval vein
- SNA – sinus node artery
- LVH – left ventricular hypertrophy
- HCM – hypertrophic cardiomyopathy

References


