Coronary fibromuscular dysplasia and sudden death - case report and literature review

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Abstract: We present a sudden cardiac death case in a 43 years old male. Death was determined by an association of coronary tree anomalies (generating a chronic hypo perfusion of the posterior and lateral diaphragmatic wall of the left ventricle) and coronary fibromuscular dysplasia (FMD). A review of recent literature revealed that coronary FMD is an extremely rare (or underreported) pathologic entity, only 16 cases being reported.

Key words: coronary fibromuscular dysplasia, myocardial infarction, sudden cardiac death

Fibromuscular dysplasia (FMD) is considered to be a non-atherosclerotic and non-inflammatory disease which affects small-medium caliber vessels by causing a luminal narrowing; usually affected are renal and carotid arteries and only rarely other arterial territories such as are abdominal, iliac and coronary vessels (very rare). We present in this article a case of intimal fibroplasia affecting coronary vessels in a male and also a brief literature review about this particular entity.

Case report

While playing a foot tennis game with friends, a 43 years old man, suddenly collapsed. An ambulance arrived at the scene ascertained a cardio-respiratory arrest, started resuscitation and transported him to an Emergency Hospital, where resuscitation efforts where continued but with no effects. A forensic autopsy was performed the next day. The relatives did not provide significant information about his previous medical record. The autopsy revealed the presence of scattered sub pleural and sub epicardial pinpoint hemorrhages, liquid blood and visceral blood pooling, moderate cerebral edema. Toxicological investigations from blood and urine were negative. In the pericardial fluid CK-MB was 941 U/L. The dissection of the heart provided more significant details.

Gross pathology and heart dissection

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1. **Left coronary artery (LCA)**

At its origin, behind the pulmonary trunk, the LCA appeared firmly covered (fig. 1) by a thick, dense and rigid, epicardial layer (fibrous pericarditis was suspected); superficial to that functionally limiting fibrous covering, the cardiac nerves and also lymph vessels and nodes were evidenced, the later supporting the presence of an epicardial inflammatory process.

The (left) circumflex artery (CxA) coursed inferior to the left atrial appendage LAA where it sent off a circumflex atrial artery that continued, covered the great cardiac vein, to distribute to the posterior wall of the left atrium. At the level of the left (obtuse) border of the heart, the CxA sent off a descending left ventricular branch supplying the anterior part of that border and ended with the left marginal artery that descended on the posterior aspect of the obtuse border.

The dissection of CxA revealed the presence of multiple subintimal atheroma deposits, with different degrees of calcification that reduce that lumen as much as 80%.

2. **The right coronary artery (RCA)**

On the diaphragmatic surface of the heart, at the crux cordis, the RCA divided, sending of the posterior interventricular artery (PIVA) and a left retroventricular artery (RVA), both appearing with a degree of atrophy. From the initial segment of the left RVA, from proximal to distal, the first two posterior septal artery(ies) PSA and the atrioventricular node artery AVNA left and coursed within the interventricular septum and the triangle of Koch, respectively.

3. **The hypovascular area**

On the diaphragmatic surface of the heart, both coronary arteries respected the left part of the coronary groove by not sending within it any arterial branch, thus, at the base of the left ventricle the coronary groove was segmentary occupied only by the great cardiac vein.
emptying into the coronary sinus (fig. 2). Inferior to that arterial-free segment of the coronary groove a triangular surface on the postero-lateral wall of the LV appeared as being hypovascular, being supplied only by thin branches (fig. 2) from:

- the terminal part of the left RVA;
- branches of the left marginal artery, with a segmental distribution.

The dissection of the heart revealed the presence of an extensive myocardial infarction scar, located on the posterolateral aspect of the left ventricle, from the apex up to the base. The pearly white cicatricial tissue was non homogenous, in places having an insular aspect (Fig 3).

**Histopathology**

The selected specimens were formalin-fixed and paraffin-embedded. Sections were cut at 5 microns and stained using the standard H&E, van Gieson and Weigert. All slides were examined and photographed on a Zeiss AxioImager A1 microscope. Digital images acquired with Zeiss Axios Vision program have been processed and analyzed with ACDSee Pro Photo Manager 3.0, running under Windows XP Professional.

**Fig. 2** Hypovascular area in the circumflex artery territory where infarct sequelae were found. On the diaphragmatic surface of the heart in the left side of the coronary groove there lack the arterial content (*): a hypovascular triangle in the postero-lateral wall of the left ventricle lining the coronary groove has its opposite angle in the infarct area. Hypoplasic and even atrophic arteries supply the area, emerged (arrowheads) from the left marginal artery (1) and the left retroventricular artery (3). The right coronary artery (2) sent the left retroventricular artery (3) and the posterior interventricular artery (4).

*5.coronary sinus.*

**Fig. 3** Myocardial infarction sequelae (2-3 months) in the posterior lateral area of left ventricle (white arrow). Left ventricular concentric hypertrophy. Right ventricular enlargement.
The microscopic examination confirmed the presence of a wide area of post myocardial infarction scarring in the left ventricle, with massive replacement of muscular fibers by a relatively dense collagen net, with very few residual cardiomyocytes, and areas where myocardial cells were replaced by mature adipose cells.

It also revealed the presence of fibromuscular dysplasia present both in sub-epicardial and intramural coronaries.

The dysplastic phenomena (fibroblastic and smooth muscle cell proliferation with frequent disruptions of the intima) were widespread and intense, determining a considerable reduction of the coronary lumen (Fig 4-6).

**Literature review**

The etiology of FMD is currently unknown [1], although genetic, hormonal, and mechanical factors have been suggested [2] FMD probably is not a single entity but more likely more similar diseases with different etiologies and similar phenotypic expression [3].

A genetic autosomal dominant inheritance with variable penetrance has been proposed [4] despite the absence of large FMD-
affected pedigrees.

Because more often women are affected by FMD a connection between estrogens and this disease had been proposed but not yet proved. It was noticed the risk of FMD being more elevated in smokers, patients with arterial hypertension, and vasa vasorum disorders [5,6]. Scientists recently found FMD to be a major clinical feature, in addition to skin and joint abnormalities, in variants of Ehlers-Danlos syndrome (EDS) [7].

First descriptions of FMD used the term fibroplasia and fibromuscular hyperplasia. In 1958, McCormick reported a histopathological description of fibromuscular hyperplasia in four patients with renovascular hypertension.

In 1965 Hunt depicted the fact that this disease is heterogeneous and not always associated with hyperplasia and used the term “fibromuscular hyperplasia” [8].

Even if in last few years different FMD classifications had been proposed the one in use remains that made by Harrison and McCormack in 1971, which differentiates three main types: intimal fibroplasia (10%), medial dysplasia with three subtypes (medial dysplasia, paramedial dysplasia and medial hyperplasia – 75-80% of all FMD cases) and adventitial fibroplasia (less than 1% of all FMD cases) [9,10].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of cases reported</th>
<th>Gender</th>
<th>Age</th>
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<tr>
<td>Siegel et al [14]</td>
<td>1991</td>
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<td>10</td>
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<tr>
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<td>M</td>
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<tr>
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<td>2</td>
<td>F</td>
<td>17,14</td>
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</tr>
<tr>
<td>Ropponen et al [18]</td>
<td>1999</td>
<td>1</td>
<td>F</td>
<td>42</td>
<td>Intimal protuberances (polyps)</td>
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<tr>
<td>Lee et al [19]</td>
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<td>1</td>
<td>M</td>
<td>24</td>
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<tr>
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<td>1</td>
<td>M</td>
<td>3</td>
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<td>M</td>
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Table 1: Cases of intimal coronary fibroplasia (search by Google Scholar, Scirus, PubMed)

Kincaid et al. realized a series of histopathologic-angiographic correlations in FMD; they described four main angiographic types: multifocal, with multiple stenoses, ("pearl necklace" 62%), tubular, with long, concentric stenosis (14%), focal, with a single stenosis of less than 1 cm (7%), and mix stenosis (21%). All cases with multifocal stenosis were associated with medial FMD whilst tubular and focal were not associated with any histopathological type [11].
In intimal fibroplasia, coronary intima appears with focal, variable thickenings due to mesenchymal cells (myofibroblast) and fibrous tissue conglomerates; intimal thickness can be concentric or eccentric, sometimes polypous; internal elastic lamina can be fragmented focally; media and adventitia are normal \[12, 13\].

Coronary FMD however is only rarely described, only a few cases \[12, 13, 14-26\] (Table 1) being presented in English speaking medical literature (searches on PubMed, Google Scholar, and Scirus). Often, coronary arteries are co-interested in multi arterial FMD involvement (usually together with renal or carotid arteries).

Their involvement can be epicardial \[26-28\] or intramural \[29-32\]; both can lead to sudden cardiac death throughout ischemic or arrhythmic mechanisms; other causes of sudden death due to FMD are those resulted from cerebrovascular FMD (by hypoperfusion, emboli, thrombosis or ruptured aneurysms), mesenteric ischemia or renal complications (renovascular hypertension, renal insufficiency) \[33\].

The need for a better knowledge created Fibromuscular Dysplasia Society of America (www.fmdsa.org) which offers a wealth of information for patients and physicians. Also an International Registry for Fibromuscular Dysplasia is now set in seven centers in US and one in Europe \[1\].

Conclusions

Fibromuscular dysplasia FMD of the coronary arteries intima is a rare finding. We have reviewed 16 similar cases with a female dominance. The case presented involved a 43 years old with coronary FMD associated to coronary tree anomalies which determined a chronic hypoperfusion of the posterior and lateral diaphragmatic wall of the left ventricle.

The capacitance of the subepicardial coronaries was markedly reduced by a combination of inborn anomalies (hypovascular area determined by a asymmetric topographic distribution of CxA branches) and acquired ones (patch of dense and rigid fibrous pericarditis compressing LCA, multiple subintimal atheroma deposits, with different degrees of calcification, that reduced considerably the coronary lumen), diminishing considerably the ability of subepicardial coronaries to fulfill their role: storing blood during systole and making it available in the diastole for the perfusion of the myocardial muscle through the intramural coronary branches. Added to that, coronary FMD further amplifying the myocardial hypoirrigation.

We consider that smooth muscle cell development within the intima of the coronary arteries may be explained by migration from the media or cellular differentiation of fibroblasts.

We could also advance the hypothesis that the chronic mechanic stress determined by the abnormal blood flow generated by the inborn and acquired anomalies of subepicardial coronaries could be at the origin of the dysplastic alteration of the coronary structure described by FMD.

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