Sudden cardiac death in non-atherosclerotic and non-inflammatory intimal cellular proliferations. A case report

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Abstract: Non-atherosclerotic and non-inflammatory intimal cellular proliferations are considered a non-homogenous group of pathological diseases usually affecting small and medium caliber arteries; they are mostly idiopathic and it is believed that some types are precursor processes in the pathogenic chain of atherosclerosis. Fibromuscular dysplasia is defined as an idiopathic, segmentary, non-inflammatory and non-atherosclerotic condition of the arterial walls, leading to stenosis in small and medium arteries. Although the etiology is unknown, potential causes may include platelet derived growth factor, fibroblastic growth factor, epidermal growth factor, kinins, angiotensin type II anomalies. The correlation between fibromuscular dysplasia and sudden cardiac death isn’t often found, only nine cases being reported in the scientific literature in the last years. We present in this article five cases of sudden cardiac death associated with fibromuscular dysplasia and discuss some of its characteristics.

Key words: Sudden cardiac death, Intimal cellular proliferations, Growth factors

Non-atherosclerotic and non-inflammatory intimal cellular proliferations are considered a non-homogenous group of pathological diseases usually affecting small and medium caliber arteries; they are mostly idiopathic and it is believed that some types are precursor processes in the pathogenic chain of atherosclerosis [1, 2]. The structure of the normal intima includes: endothelial cells, smooth muscle cells, extracellular matrix of collagen, proteoglycans, small amounts of elastin, and occasionally, inflammatory cells [3]. There are a number of terms used for the description of non-atherosclerotic histological alterations of the intima [3, 4] (Table 1). Neo-intimal thickenings were usually described as located in arterial ramification points, accentuated in male infants and it is hypothesized that its distribution in younger ages is correlated with the distribution of atherosclerosis in adults [3].

Fibromuscular dysplasia (FMD) was first described in 1958, by McCormack who reported its histological appearance in four patients with reno-vascular hypertension. In 1965, Hunt proved that this disease represents a heterogenous condition that is not necessarily associated with hyperplasia and introduced the term of FMD [5]. Nowadays, according to OMIM #135580, FMD is defined as an idiopathic, segmentary, non-inflammatory and non-atherosclerotic condition of the arterial walls, leading to stenosis in small and medium arteries.

Khan, in 2008, has updated the FMD classification [6] by dividing it in various subtypes: intimal fibroplasia (IFP, 1-2%), medial fibroplasia (85%), medial hyperplasia (5-15%), sub-adventitial fibroplasia (20%), dissection of the media (5-10%), adventitial fibroplasia (<1%). Thomas [7] defined FMD as proliferation and disorganization of cellular and extracellular elements in the involved arterial segment. Intimal fibroplasia has a prevalence of 1–5% of all cases of FMD and is more prevalent in young women, although it can be diagnosed at any age.

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Hyperplasia Represents an increase in the cell number of a tissue or organ

Hypertrophy Represents the growth of the cells dimensions, accompanied by an increase of its function; hypertrophy and hyperplasia aren’t mutually exclusive, being frequently found together

Neo-intimal thickening (intimal cell masses, cushions) Gross examination: thickened and whitish areas, frequently present in the arterial ramifications points
Microscopy: smooth muscle cells and connective tissue;

Non-atherosclerotic intimal proliferation Lesion involving a proliferation of smooth muscle cells within the intima, without evidence of atherosclerosis and vasculitis

Intimal fibroelastosis Process of adaptation of the arterial wall to a hemodynamic or inflammatory stress, which is followed by the stimulation of the myocytes adjacent to the endothelium in order to synthesize collagen and elastin which will be deposited within the intima

Intimal fibroplasia This term refers to the fibromuscular dysplasia (FMD) type with involvement of the intimal layer

Table 1. Definitions for non-atherosclerotic histological alteration of the intima

The etiology of IFP is unknown; potential causes include platelet derived growth factor, fibroblastic growth factor, epidermal growth factor, kinins, angiotensin type II, etc.; Thomas has described a case of intimal proliferation in the smooth muscle cells of a 21 month old child exposed to maternal cocaine abuse during gestation [7] Simpson found FDM in an adult who used cocaine for five years [8]. IFP prevalence varies from 2% of all FMD cases [9] to 10% according to Behrendta [2]. On light microscopy IFP is characterized by focal nonhomogeneous intimal thickenings with increased density of myofibroblasts, and fibrous tissue; these intimal thickenings can be either concentric or eccentric or polypous; internal elastic lamina is either not affected or focally fragmented, whilst the medial and adventitial layers are normal [2, 9].

Case reports

Case 1. A 20 years old man died suddenly in his home, without witnesses, in the evening after returning from work. His personal history wasn’t significant according to its family. The medico-legal autopsy was performed the next day and found the following: marked visceral stasis, serous petechiae, massive pulmonary edema, left ventricular concentric hypertrophy with global dilation of the cardiac right chambers with decreased myocardial thickness in both right ventricle and atrium, coronary bridging of the anterior descendent coronary (LAD), hepatomegaly (2 kg). Toxicological screening for alcohol, and drugs of abuse was negative. Microscopical examination revealed the following: heart – epicardial coronary artery with muscular bridging, medial-intimal fibroplasia (Figure 1), and early stage aneurismal dilation, intramural coronary arteries with medial-intimal hyperplasia with subsequent luminal diameter decrease, patchy endocardial fibrosis, areas of interstitial fibrosis, and interstitial and perivascular fibro-lipomatosis; other organs showed nonspecific signs like visceral stasis and pulmonary edema. Death was due to acute cardio-respiratory failure caused by multiple cardiovascular anomalies with subsequent alteration of the tridimensional cardiac structure.

Case 2. A 20 year old woman, while walking with her boyfriend, complains of sudden abdominal pain and shortly after loses her conscience. She is taken to the hospital, where ventricular fibrillation is
diagnosed. Cardio-respiratory resuscitation was inefficient. Personal history was negative except some unspecific epigastric pains in the last month.

**Fig. 2.** Intimal cellular proliferation which breaks in the internal elastic lamina and affects external third of the media

**Fig. 3.** In a papillary muscle, intramural coronary branch with severe medial-intimal hypertrophy with important lumen reduction and small adjacent scar, perivascular and interstitial sclerosis

**Fig. 4.** Epicardial coronary with intimal fibroplasia, perivascular and interstitial fibrosis and fibro-lipomatosis

**Fig. 5.** Coronary branch with bridging, with collapsed lumen and moderate focal intimal fibroplasia

The medical-legal autopsy revealed the following: serous petechiae, cerebral stasis and edema, marked pulmonary stasis with areas of hemorrhage and edema, diffuse myocardial fibrosis, old myocardial infarction, myocardial hypoxia, bridging on LAD at 1,5 cm from the origin, coronary hypoplasia (left coronary, LAD, RCA, with the maximum diameter of LAD being of 1,9 mm and of RCA 1,43 mm) with luminal reduction and acute thrombosis on the LAD, thyroid increased in volume, liver and renal stasis.

Toxicological screening was negative for drugs and alcohol. Thanatochemistry found the following: CK-MB in the pericardial fluid - 393,68 U/L, LDH in the pericardial fluid - 534,27 U/L, T4 - 5,97 µg/dl (n. 4,5 - 12), T3 - 2,6 ng/ml (n. 0,79 - 1,49), TSH=10,62 µUI/ml (n. 0,49 - 4,67). Microscopical examination revealed the following: epicardial coronary arteries with nodular pattern of intimal cellular proliferation, breaking the internal elastic lamina and affecting the external third of arterial media (Figure 2); the medium sized coronary arteries had diffuse and nodular intimal proliferation; extensive endocardial fibrosclerosis and areas of myocardial fibrosis most preeminent in areas vascularized by coronary arteries with intimal proliferation, marked peri-arteriolar fibrosis; 4-6 weeks acute myocardial infarction with 3 weeks old re-infarction, myocardial hypoxia, interstitial fibro-lipomatosis, and interstitial edema.
Other findings were anisofollicular goiter, thymic hypertrophy with interstitial sclero-lipomatosis and numerous pathological Hassall bodies, adenohypophysis with a small area of inter-acinar fibrosclerosis, chronic pulmonary stasis, visceral stasis, and pulmonary edema. Death was due to the acute cardiac failure, subsequent to a complicated acute myocardial infarction in a patient with numerous congenital and acquired anomalies (myocardial bridging, intimal fibroplasia, hypothyroidism, pathological Hassall bodies, and chronic pulmonary stasis).

Case 3. A 48 years old man complains of sleepiness and dizziness while being at home. He is A couple of hours later is found unresponsive in the bedroom. He is hospitalized in a deep coma (GCS = 3) and dies 46 hours later. The medical-legal autopsy found the following: visceral anemia, pulmonary edema, dilative cardiomyopathy. Toxicological screening was negative for drugs and alcohol. Thanato-chemistry: CK-MB in the pericardial fluid - 677,13 U/L LDH in the pericardial fluid - 1270,92 U/L.

Microscopical examination revealed: intra-papillary coronary artery with marked medial-intimal hypertrophy with important luminal reduction and a small underlying fibrous scar (Figure 3); moderate coronary atherosclerosis, peri-vascular sclerosis, myocardium with areas of sclerosis and fibro-lipomatosis which dissociates and focally replaces myocardial muscular fibers, extensive myocardial hypoxia, moderate endocardial and underlying interstitial fibrosis. Other findings were: visceral stasis, pulmonary edema, chronic liver stasis, chronic severe hepatitis with cirrhogenic tendency, chronic interstitial nephritis, chronic sclerogenic pancreatitis. Death was caused by acute cardio-respiratory failure due to altered myocardial structure caused by congenital and acquired coronary anomalies (intimal fibroplasia, coronary atherosclerosis).

Case 4. A 35 years old male is found dead in his home by his family. Personal history is negative. Medical legal autopsy found the following: marked visceral stasis, meningo-cerebral edema, pulmonary edema, diffuse myocardial fibrosis, endocardial and epicardial fibrosis, incipient aorto-coronary atherosclerosis, coronary hypoplasia (left coronary, left circumflex - LCx, LAD), myocardial bridging on LAD at 1,5 cm from its origin (length - 0,8 cm thickness - 0,2 cm), beyond which point the coronary becomes filiform.

Toxicological screening was negative for drugs and alcohol. Thanato-chemistry: CK-MB in the pericardial fluid - 456,68 U/L LDH in the pericardial fluid - 3217,76 U/L. Microscopical examination revealed: epicardial coronary branch with intimal fibroplasia (Figure 4); intramural coronary branches with incipient lesions of atherosclerosis; small intramural coronaries with important media hypertrophy vascular wall fibro-hyalinosis; increased perivascular and interstitial fibrosis and fibro-lipomatosis displacing myocardial muscular fibers, myocardial hypoxia, severe granular dystrophy of subendocardial cardiomyocytes, endocardial and papillary fibrosis; other organs showed nonspecific signs like visceral stasis and pulmonary edema. The death was due to the acute cardio-respiratory failure due to severe myocardial structure alterations in a person with coronary anomalies (coronary hypoplasia, intimal fibroplasia, and myocardial bridging).

Case 5. A 41 years old male, suddenly becomes unconscious in a public place. He is taken to the hospital while being in unresponsive cardio-respiratory arrest. Personal history was unavailable. The medicolegal autopsy found the following: visceral stasis, serous petechiae, cardiomegaly, myocardial fibrosis, myocardial bridging on the distal third of the LAD with proximal atherosclerosis. Toxicological screening was negative for drugs and alcohol. Thanato-chemistry: CK-MB in the pericardial fluid – 633.8 U/L, LDH in the pericardial fluid - 3379 U/L. Microscopical examination found: myocardial bridging, moderate focal intimal fibroplasia (Figure 5), small areas of myocardial fibrosis myofibrillar disorganization with neighboring hypertrophied cardiomyocytes, leukostasis. Other organs showed unspecific changes. Death was due to acute cardio-respiratory failure due to myocardial fibrosis determined by congenital and acquired coronary anomalies (bridging, intimal fibroplasia, coronary atherosclerosis).

Discussion

Intimal cellular proliferations (ICP) are not a clinical-pathological entity. They represent a histopathological feature, and when confronted with such a discovery diagnostic conclusions can only be drawn by correlating histopathological results with the type of arteries involved, age, sex, clinical features, necropsy
results and other laboratory tests. ICP can be idiopathic or can be found (sometimes as a less frequent feature) in [2]: intimal fibroplasia (a type of FMD), systemic lupus erythematosus, neurofibromatosis type I, Buerger disease, Kohlmeier-Degos disease, vasculopathies related to connective tissue diseases, giant cells arteritis, Wegener granulomatosis, panarteritis nodosa, chronic arsenic intoxication, Churg-Strauss syndrome, Henoch-Schonlein purpura. In a case report [10], Siegel suggests a clinical approach of intimal hyperplasia cases and makes a wide discussion of conditions prone to be associated with ICP: intimal fibroplasia, idiopathic arterial calcification of the infant (IACI), progressive arterial occlusive disease (Kohlmeier-Degos), Moyamoya disease, chronic arsenic intoxication, neurofibromatosis, tuberous sclerosis, congenital rubella syndrome, homocystinemia, Kawasaki disease, panarteritis nodosa, coronary arteriopathy after cardiac transplant. Keina [11] includes in the differential diagnosis diseases like the Down syndrome or sickle cell anemia.

In the last five years there were described in the medical English literature nine cases of sudden cardiac death (SCD) associated with ICP [7, 12, 13, 14, 15, 16, 17]. Out of this nine cases, one was associated with intrauterine exposure to cocaine [7], three cases with the body-building and steroids intake [17] and one case with hypertrophic cardiomyopathy (HCM) [13]. The latter is similar to our first case – they both had intimal proliferation of the intramural branches, exposed to the high systolic pressure (almost always associated with HCM); our case also had a medial-intimal proliferation of an epicardial coronary, which can be related to the coexistent bridging from this level.

In the five cases we have studied, we haven’t noticed systemic arterial signs of ICP. We only have localised types of ICP, involving the coronary arteries. Nor the renal arteries (the most frequent site for fibroplasia, especially of the medial type) or other examined ones (cerebral, pulmonary, intrahepatic) had ICP. The involvement of a single coronary was noted in three cases, and the involvement of multiple coronaries in two cases; in two cases there were only involved epicardial branches, in other two had both epicardial and intramural branches, and in a single case only an intramural branch located within a papillary muscle was found with associated with FMD. Out of the nine cases described in the literature, seven showed anomalies only in the coronary arteries [13, 14, 15, 16, 17] involving mostly the major epicardial branches [7, 12, 14, 15, 16, 17], and in some of them coexisting intramural branches anomalies (ICP) [7, 16, 17]. In three of our cases the proliferation is located only in the intimal layer, whilst in the other two it coexists with a proliferation of the media (in the same arterial segment). In the literature, intimal proliferation is by far the most frequent occurrence [7, 13, 14, 15, 17]. The nodular pattern of intimal proliferation was found solitary in one case and mixed with diffuse intimal proliferation in another one. Both patterns were described in the literature [7, 16, 17].

In four cases coronary anomalies were associated with marked perivascular and interstitial fibrosis and in three of them there was described underlying myocardial scars, results similar with those obtained by [15, 16]. Microscopical examination of all five reported cases showed a higher degree of perivascular fibrosis than expected for the age, sex and cause of death (SCD). Regarding the interstitial fibrosis, although it was severe, it wasn’t present in a higher extent than should have been for the age, sex and cause of death (SCD); for the comparison we was used the algorithm provided by Curca CG et al [18]. The myocardial alteration score was 2.45, similar to the one obtained by the abovementioned authors in their analysis of sudden cardiac death in young adults. The presence of a higher degree of myocardial fibrosis, both perivascular and interstitial, favors an increase in the electrical heterogeneity of the myocardium with a subsequent increase in QTc dispersion which leads to a higher predisposition for ventricular tachyarrhythmias throughout reentry mechanisms. In four of our cases we found myocardial bridging on the LAD. In our review of the literature only a single case presented this association. [12]. Some authors [19] believe that the appearance of the intimal proliferation above the bridging is determined by the changes in various pressure types in the bridged artery during systole: a local increase in the hydrostatic pressure and a marked decrease of the superficial tension in the area where the artery curves during the systolic compression favors local remodelling processes (increased apoptosis, migration and synthesis of the vascular smooth muscle cells and fibroblasts, mitotic index etc.) and local LDL deposits, both causes favoring the appearance of intimal hyperplasia and atherosclerosis. LAD is the coronary most frequently associated with hemodynamically significant myocardial bridging due to the morphological features of the adjacent myocardium (the fibers leave from the pulmonary infundibulum, the angle made by the myocardial fibers with the artery is generally more than 80°, the localization of the artery in the interventricular sulcus, etc.). Thanatoo-chemical analysis of the pericardial fluid, have shown moderate increases in CK-MB in the pericardial
As a conclusion, ICP are infrequent causes of SCD; when are associated we should always exclude other causes. ICP associated with SCD is more common on the epicardial arteries and in not usually associated with medial proliferation. ICP is usually accompanied by perivascular and interstitial fibrosis and is often associated with other cardiovascular anomalies, both congenital and acquired.

References


