

## **HYPERTROPHIC CARDIOMYOPATHY ASSOCIATED WITH POLYARTERITIS NODOSA: A CASE OF SUDDEN CARDIAC DEATH**

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### **ABSTRACT**

This case concerns a rare sudden cardiac death characterized by macroscopic and microscopic post-mortem findings of hypertrophic cardiomyopathy and polyarteritis nodosa.

A complete autopsy was carried out, and histological and histochemical methods were employed.

The cause of death was acute multifocal ischemic myocytolitic damage caused by both myocardial structural alteration attributable to hypertrophic cardiomyopathy (widespread interstitial fibrosis and multifocal myocyte disarray) and coronary arteritis attributable to polyarteritis nodosa. This is the first case in which the cause of death was attributed to both diseases.

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### **1. Introduction**

Sudden cardiac death (SCD) signifies an unexpected natural death from a cardiac cause that occurs within a short period, generally within the first hour from the onset of symptoms, in a subject without any prior condition that would appear fatal [1]. The main cause of SCD is coronary atherosclerotic disease representing about 80% of all SCDs, followed by cardiomyopathies, myocarditis, valvular disease, channelopathies and vasculitis [2-4].

Many authors highlighted that cardiomyopathies frequently causes sudden death, particularly in young people, and the hypertrophic cardiomyopathy (HCM) is considered one of the most common diseases [5,6]. Vasculitis can also be a cause of SCD and there are many reported cases in which death was ascribed to large-vessels vasculitis, as Takayasu Arteritis and Giant Cell Arteritis, or medium-vessels arteritis, as Kawasaki Disease and Polyarteritis Nodosa (PAN) [7-11].

Even if both cardiomyopathies and vasculitis are diseases well described and classified clinically and anatomically, in literature there is no evidence about the possible association of the two diseases nor are there, to our knowledge, any cases in which the presence of both pathologies were observed during post-mortem investigations.

For these reasons, we report a case study about an unusual sudden cardiac death in which the autopsy findings revealed the presence of hypertrophic cardiomyopathy and polyarteritis nodosa with coronary involvement.

### **2. Case Report**

Our case involves a healthy 33-year-old man without familiarity or any risk factors for cardiovascular pathology. He had no chronic illnesses and received no medications.

A complete autopsy was carried out, and histological and histochemical methods were employed (Hematoxylin and Eosin, Masson's trichrome).

The anatomy of the great arteries, pulmonary veins, and superior and inferior vena cava was examined and found to be normal.

A complete transverse (short-axis) cut of the heart at the mid-ventricular level followed by parallel slices through the ventricles at 1 cm intervals toward the apex was performed to evaluate the morphology of the walls and cavities.

Once the heart had been emptied of blood, the following measurements were noted. Total heart weight: 759 g; transverse, longitudinal and antero-posterior heart dimensions: 8.5, 11.5 and 10 cm, respectively.

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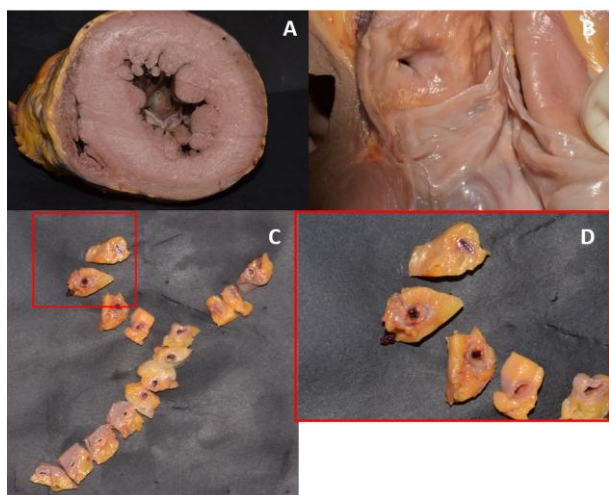
Significant concentric left ventricle hypertrophy (Figure 1a); bulging of the subaortic interventricular septum (2.5 cm) (Figure 1b).

The size, shape, position, number, and patency of the coronary ostia were examined. The major epicardial arteries presented right “dominance”. The serial transverse sections of major coronary arteries and branches showed an intramural course of the anterior interventricular artery with a myocardial bridge (3 mm). The distal and circumferential branches presented a lumen dilation associated with intimal myxoid thickening (Figure 1d). Histological sections of the coronary arteries showed eccentric obstruction of the lumen due to fibromyxoid plaque with widespread granulomatous lymphoplasmacytic infiltration and rare giant multinucleated histiocytes; the inflammatory lesions regarded adventitia and media and were associated with alteration of elastic membranes and microaneurysm (Figure 2a, b).

Histologic examination of the myocardium revealed widespread interstitial fibrosis and multifocal myocyte disarray (Figure 3a); hypertrophied cardiac myocytes, which often presented double and dysmorphic nuclei (Figure 3b); small post-ischemic myocytolysis foci with early granulocyte infiltration in the interventricular septum.

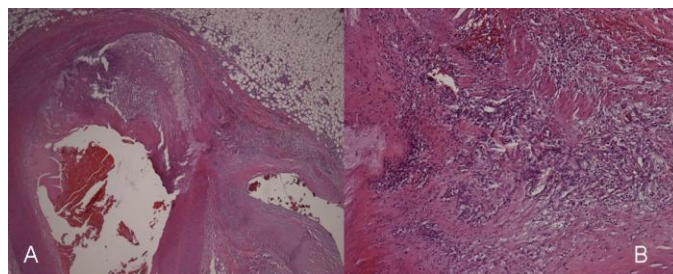
A histologic examination of the lungs revealed haemorrhagic oedema and emphysema; pulmonary vessels showed alterations ranging from medial hypertrophy to occlusive intimal hyperplasia (stage II-IV of Heath-Edwards classification). A histologic examination of the kidneys disclosed vascular congestion associated with interstitial sclerosis and sub-obstructive intimal hyperplasia of arcuate arteries, interstitial nephritis and deposition of eosinophilic hyaline material in glomerular architecture.

Genetic analysis on DNA extracted from formalin-fixed paraffin-embedded post-mortem myocardial tissue was performed to verify the mutations of MYH7 and MYBPC3, commonly involved in hypertrophic cardiomyopathy, and CECR1, recently associated with polyarteritis nodosa. The analysis resulted negative.

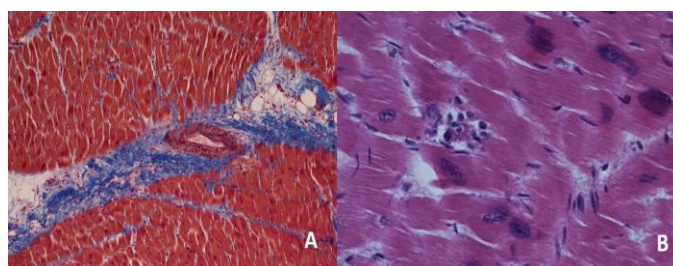


**Figure 1 - a. Short-axis view of gross transverse cardiac section showing the concentric left ventricle hypertrophy; b. Asymmetrical appearance due to "bulging" of the subaortic septum (2.5 cm); c.**

**serial transverse sections of major coronary arteries and branches; d. The insert shows the distal and circumferential branches lumen dilation, associated with intimal myxoid thickening.**



**Figure 2 - a. Histological sections of the coronaries showing eccentric obstruction of the lumen due to fibromyxoid plaque (Haematoxylin and Eosin, x100 magnification); b. The insert shows the fibromyxoid plaque with widespread granulomatous lymphoplasmacytic infiltration and rare giant multinucleated histiocytes (Haematoxylin and Eosin, x200 magnification).**



**Figure 3 - Microscopic findings. a. Interstitial fibrosis and multifocal myocyte disarray (Masson trichrome stain at x100 magnification); b. hypertrophied cardiac myocytes, which dysmorphic nuclei (Haematoxylin and Eosin, x100 magnification).**

### 3. Discussion

Cases of SCD caused by hypertrophic cardiomyopathy are rather common in literature, while cases of SCD related to coronary nonatherosclerotic disease are rare. The reported case is a rare presentation of sudden cardiac death characterized by macroscopic and microscopic post-mortem findings of hypertrophic cardiomyopathy and polyarteritis nodosa.

The cause of death was an acute multifocal ischemic myocytolitic damage caused by both myocardial structural alteration attributable to HCM (widespread interstitial fibrosis and multifocal myocyte disarray) and coronary arteritis attributable to PAN.

Hypertrophic cardiomyopathy is a heart disease usually characterized by a non-dilated left ventricle, a normal or increased ejection fraction and an asymmetrical severe hypertrophy commonly involving the basal interventricular septum subjacent to the aortic valve.

The histological findings are represented by hypertrophied cardiac

myocytes showing a bizarre shape and pleiotropic nuclei, a loss of normal parallel alignment with the characteristic pattern of “disarray” that generally involves >10% of the myocardium affecting often the interventricular septum. Moreover, the increased interstitial fibrosis is another common feature.

HCM is a common cause of sudden death in young adults and it can occur during both routine daily tasks and even mild physical activities [6]. The clinical manifestations of the disease, which can also be causes of sudden death, are related to structural alteration of the ventricular cavity with consequent anomalies of the ejection function (due to both left ventricular outflow tract obstruction and diastolic ventricular dysfunction) or ischemic episodes related to increased myocardial mass or to malignant arrhythmias resulting from fibrous substitution [12].

Several authors highlight that HCM is related to genetic disorders with an autosomal dominant pattern. Many causal genes are associated to this disease and the most common are MYH7 and MYBPC3, encoding respectively beta-myosin heavy chain and cardiac myosin binding protein C, that together are responsible for approximately half of the familial HCM.

Although involvement of other genes (i.e. TNNI3, TPM1, and others) has been highlighted, in 40% of subjects the causal gene has not been identified, especially when HCM occurred in sporadic cases and small families [12].

In SCD, fields are also included in the vasculitis along with PAN which represents a cause of sudden death in very few cases showing, generally, an involvement of isolated coronaries [8].

PAN is a rare disease with an incidence rate ranging from 0 to 1.6 cases per million in European countries, characterized by a systemic necrotizing arteritis which commonly affects the kidneys, gastrointestinal tract, skin, nerves, joints, muscle and cardiovascular system. It is a disease poorly understood and the diagnosis is a clinical challenge despite classification criteria, because the patients frequently present unspecific signs as fever, myalgia or arthralgia, cutaneous lesions, gastrointestinal symptoms, hypertension, renal proteinuria and haematuria. The histopathological findings are inflammatory infiltration with fibrinoid necrosis, followed by scarred granulation tissue, and sectorial lesions in medium and small muscle-like arteries.

In most SCDs related to PAN, a myocardial infarction due to coronary occlusion or thrombosis associated with stenosis and/or coronary aneurism was highlighted. In few cases, a coronary spasm showing myocardial infarction without coronary stenosis was suggested [13]. Recently, it was reported that this vasculitis could be associated to a deficiency of adenosine deaminase 2 (ADA2) due to a recessive mutation in the related encoding gene CECR1 [14].

In literature, there is only one case reporting the association of both diseases in which the diagnosis has been clinical and there was no coronary involvement from PAN [15]. The presented case, to our knowledge, is the first showing hypertrophic obstructive cardiomyopathy with coronary involvement due to polyarteritis nodosa.

The macroscopic and microscopic analysis showed characteristic diagnostic patterns through which two unidentified and non-clinically

manifest pathologies were diagnosed post-mortem.

The post-mortem genetic tests were performed as the routine procedures in the investigation of any sudden unexpected death recommend (molecular autopsy). The analysis resulted negative for mutation of the most common genes involved in HCM, as well as the gene recently associated with PAN, demonstrating that the knowledge about the etiopathogenesis of both disorders needed other studies to provide an early diagnosis and clinical management, especially in family cases, and to prevent the sudden death.

Lastly, the case leads us to ask if the occurrence of both pathologies, rather than casual coexistence, could be a “pathological association” that may be attributed to a common pathogenesis. In order to prove this hypothesis, we encourage the publication of other reports and new research involving this pathological association.

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