Case 03/12 – A 41-Year-Old Female Patient with Hypertrophic Cardiomyopathy and Congestive Heart Failure

Fernando Luiz de Melo Bernardi e Luiz Alberto Benvenuti
Instituto do Coração (InCor) HC-FMUSP, São Paulo, SP - Brazil

A 41-year-old female patient with hypertrophic cardiomyopathy was hospitalized for palpitations and severe dyspnea. She had a history of tachycardic palpitations accompanied by diaphoresis and paleness since 30 years of age; at 33 she started to present with dyspnea on heavy exertion, when she had an episode of syncope and was referred to InCor-HCFMUSP (2003).

On physical examination (August 28, 2003), her heart rate was 74 bpm, blood pressure 130 / 70 mmHg; pulmonary auscultation normal; cardiac auscultation normal; abdominal examination normal; no lower limb edema was observed; her right dorsalis pedis pulse was not palpated; mild jugular venous distension at 45° was observed. Her laboratory tests were normal (Table 1).

ECG (Feb 2013) showed normal sinus rhythm, rate of 65 bpm, PR = 159 ms, DQRS = 87 ms, QT = 434 ms, left atrial and left ventricular overload with strain pattern (Figure 1).

Echocardiogram (Jul 27, 2003) revealed septal hypertrophy (18 mm); posterior wall thickness of 11 mm; left atrial enlargement (45 mm); normal left ventricular wall motion and ejection fraction of 80% (Table 2).

Electrophysiological study (Sep 12, 2003) showed no accessory pathway. The intervals measured were AH = 66 ms; HV = 51 ms, PW = 470 ms. Although no accessory pathway had been demonstrated, jump and junctional echo were detected; the extrastimuli in the apex and right ventricular outflow tract did not trigger arrhythmias.

Exercise test (Sep 16, 2003) showed ST-segment abnormalities in the presence of left ventricular overload; no arrhythmia was observed.

Tilt test (Sep 16, 2003) was negative for a cardioinhibitory response or vasodepression. The initial blood pressure was 110 / 66 mmHg and 102 / 60 mmHg at 70° inclination; the initial heart rate was 80 bpm and remained unchanged up to 70° inclination.

The 24-h Holter monitoring did not show ventricular arrhythmia and only six isolated atrial extrasystoles. The symptoms reported during examination were racing heart, chest pain, shortness of breath and dizziness which did not correlate with ECG changes.

The patient progressed with short-duration paroxysmal palpitations on propranolol 40 mg.

A "Looper" was installed, which recorded nodal reentrant tachycardia (Apr 16, 2004) with a rate of 187 bpm.

In April 24, 2004, she sought medical care and was diagnosed with nodal reentrant tachycardia with a rate of 212 bpm, which was reverted with intravenous adenosine. The propranolol dose was increased to 160 mg daily. Due to frequent episodes of tachycardic palpitations, a new electrophysiological study was indicated (June 2005), which revealed double nodal pathway on programmed atrial stimulation with induction of tachycardia by nodal reentry, initially with an atrioventricular conduction of 2:1 and later of 1:1. Six radiofrequency applications were delivered in zones 3 and 2 of the slow pathway; junctional rhythm was observed during the applications. Programmed atrial stimulation and isoprenaline showed changes in the slow pathway. The procedure was considered successful.

The patient remained with tachycardic palpitations and atrial fibrillation was detected in one episode; oral anticoagulation with amiodarone was started (2007).

Echocardiogram (2007) remained unchanged (Table 2).

Palpitations persisted with episodes of worsened dyspnea, which occurred even at rest and the patient was hospitalized twice for electrical cardioversion.

ECG (May 2009) showed atrial fibrillation, mean heart rate of 80 bpm, and left ventricular overload (Figure 2).

A new echocardiogram showed moderate left ventricular dysfunction (Table 2).

Holter monitoring at that time revealed atrial fibrillation as the baseline rhythm.

The patient was hospitalized again in December 25, 2010, with severe dyspnea. She was diagnosed with acute pulmonary edema and thromboembolization to her left upper limb, and underwent thromboembolectomy via brachial artery catheterization.

Chest radiography showed cardiomegaly and pulmonary congestion.

Keywords

Heart failure; cardiomyopathy,hypertrophic; tachycardia, paroxysmal; ventricular dysfunction, left.

Mailing Address: Vera D. Aiello
InCor – Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: anpvera@incor.usp.br

Table 1 – Laboratory tests

	Jul. 2003	2007	2010	Feb 20, 2011	Mar 3, 2011	Mar 9, 2011
Hb (g/dL)	15.3	15.6		14.5	15	12.3
HT (%)	44	45		44	45	39
White blood cells/mm³	9700	8400		18610	13610	10160
Neutrophils (%)	-	-		93	83	84
Eosinophils (%)	-	-		0	1	1
Lymphocytes (%)	-	-		4	10	11
Monocytes (%)	-	-		3	5	4
Platelets/mm³	232000	222000		225000	344000	296000
Creatinine (mg/dL)	0.9	0.96		1.18	1.11	0.96
BUN (mg/dL)	19	47		45	54	42
Sodium (mEq/L)	140	138		142	134	128
Potassium (mg/dL)	4.3	4.9		3.4	4.7	4.7
TSH (U/L)		4.01	10			-
Cholesterol (mg/dL)	140	153				
HDL-C (mg/dL)	48	45				
LDL-C (mg/dL)	71	89				
Triglycerides (mg/dL)	106	95				
Blood glucose (mg/dL)	88	83				
PT (INR)				3.6	1.2	1.1
APTT (rel)				1..18	1.37	-
Lactate (mg/dL)				39		17
ALT (U/L)		50		439	95 (Feb 25)	
AST (U/L)		29		347	216 (Feb 25)	

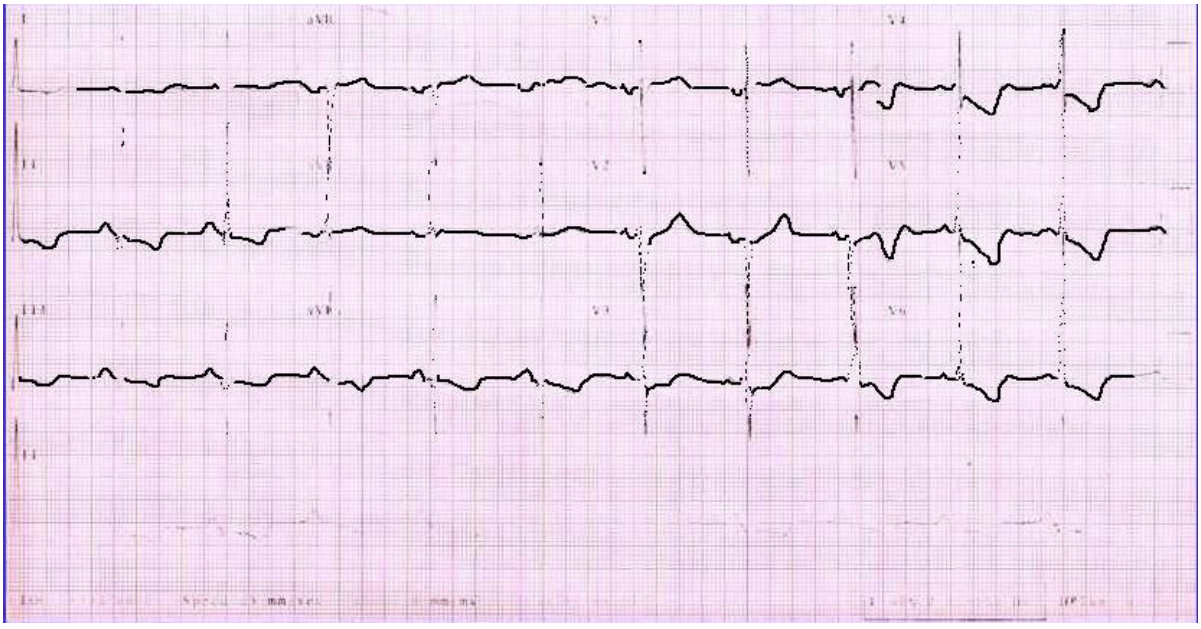

Figure 1 – *ECG: left atrial and left ventricular overload with strain pattern.*

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Table 2 – Echocardiographic progression

	2003	2007	2009	2011
Aorta (mm)	29	29	37	30
Left atrium (mm)	45	50	51	55
Right ventricle (mm)	Normal	12	24	34
Septum (mm)	18	18	16	15
Posterior wall (mm)	11	11	10	11
LV diastole (mm)	55	38	35	42
LV systole (mm)	22	27	28	34
LVEF (%)	80	56	45	35
LV	Hypertrophic	Hypertrophic	Hypertrophic	Hypertrophic
Wall motion	Normal	Normal	Diffusely low; worse septal	Diffusely low; worse septal
Mitral valve	Normal	Normal	Normal	Normal
Tricuspid valve	Normal	Normal	Normal	Severe regurgitation
LV filling	E<A	pseudonormal	- AF	- FA
Syst blood pressure pulmonary art. (mm Hg)	Normal	Normal	Normal	70

AF- atrial fibrillation; Syst blood pressure pulmonary art.- systolic blood pressure of the pulmonary artery.

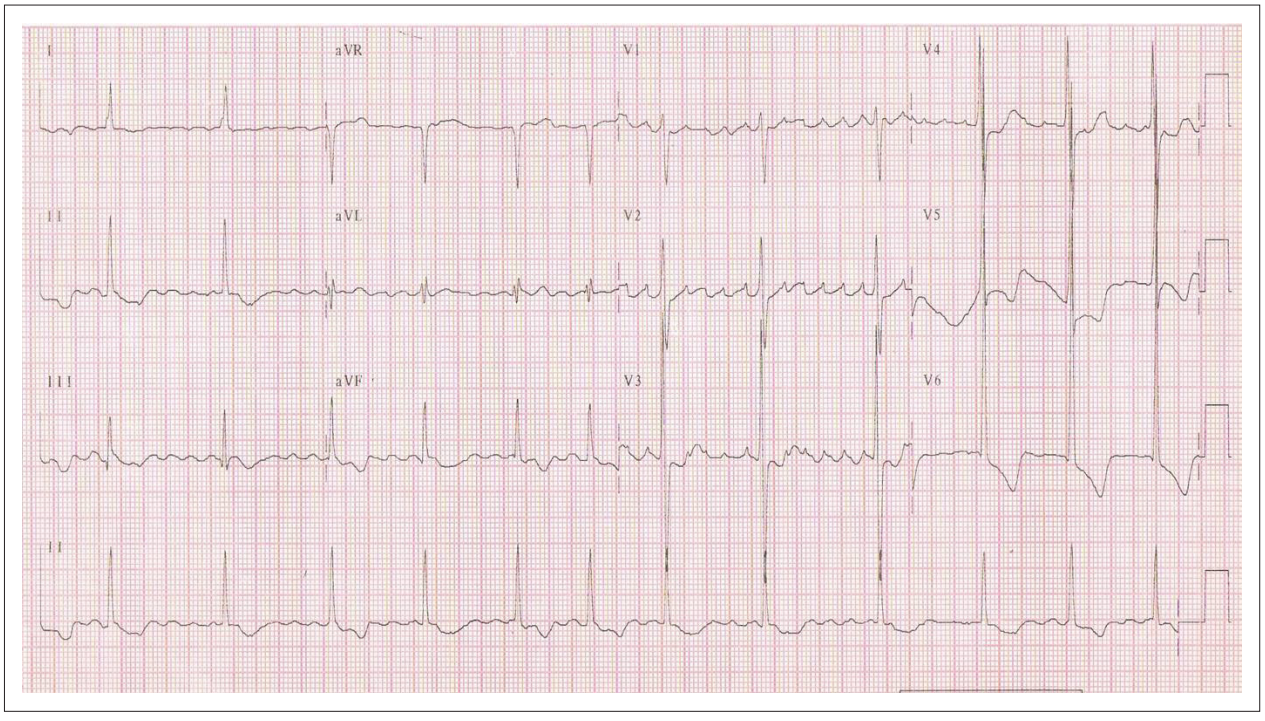

Figure 2 – *ECG: atrial fibrillation, rate and left ventricular overload.*

She was on carvedilol 25 mg; amiodarone 200 mg; furosemide 20 mg; losartan 25 mg; pentoxifylline 800 mg; omeprazole 20 mg, and warfarin.

Finally, she sought emergency medical care for an episode of palpitations accompanied by severe dyspnea for 30 minutes.

Laboratory tests revealed hypothyroidism (Table 1).

Physical examination (February 19, 2011) showed tachydyspnea, profuse diaphoresis and cold extremities; jugular venous distension at 45º; respiratory rate of 40 breaths per minute; tachycardia 140 bpm; blood pressure 120 / 80 mmHg. Cardiopulmonary auscultation revealed crackles up to the apex of both lungs; irregular cardiac rhythm; diminished S1 and S2; no murmurs.

Abdominal examination was normal. No lower limb edema was present.

The patient was diagnosed with acute pulmonary edema triggered by fibrillation with fast ventricular response; electrical cardioversion was attempted three times with progressive energies of 100 J, 200 J and 300 J, unsuccessfully. The patient improved with heart rate control and the use of vasodilators and diuretics.

ECG (February 19, 2011) revealed atrial fibrillation; mean rate of 138 bpm; dQRS of 163 ms; SÂQRS +90º; intraventricular conduction disturbance and left ventricular overload (Figure 3).

Laboratory tests revealed leukocytosis (Table 1). Chest radiography (February 21, 2011) showed consolidation in right lung base.

Echocardiogram showed moderate left ventricular dysfunction, pulmonary hypertension and right ventricular dilatation (Table 2).

Pulmonary computed tomographic angiography (February 22, 2011) did not show arterial filling defects. There were consolidation areas in the basal segments of the lower lobes; lines suggestive of atelectases in middle lobe and both bases; pleural effusion on the right side with fissure involvement; and moderate pericardial effusion.

Ultrasound (February 23, 2011) showed normal liver, ectasia of the superior vena cava and suprahepatic vein; normal kidneys and urinary system; moderate ascites.

During follow-up, the patient developed fever, productive cough and leukocytosis. Antibiotic therapy with ceftriaxone was started. She was hemodynamically compensated; however, she had two episodes of ventricular tachycardia that required electric cardioversion. The use of an implantable cardioverter-defibrillator was indicated. While awaiting the procedure, the patient presented with bradycardia followed by pulseless electrical activity irresponsive to resuscitation procedures and died on March 9, 2011.

Clinical aspects

Hypertrophic cardiomyopathy (HCMP) is an inherited autosomal dominant primary myocardial disorder characterized by inadequate hypertrophy of the cardiac muscle. HCMP is the most common primary myocardial disease, with an incidence of 1:500, and may manifest at any age[1-4].

HCMP is considered a "disease of the sarcomere" and its etiopathogenesis consists of the mutation of some gene responsible for the formation of sarcomere structures. Mutations have already been identified in nine genes causing HCMP, and mutation in only one of these genes is necessary for the development of the disease; the penetrance-action is of 95%[5].

The morphological findings in HCMP consist of inadequate myocardial hypertrophy, which leads to a disarray of the myocyte structures culminating in cell dysfunction, apoptosis and formation of fibrosis in the myocardial interstitium. These changes explain the pathophysiological manifestations of HCMP, which are characterized by ventricular dysfunction and arrhythmias. Ventricular hypertrophy is symmetrical in 50% of the cases;

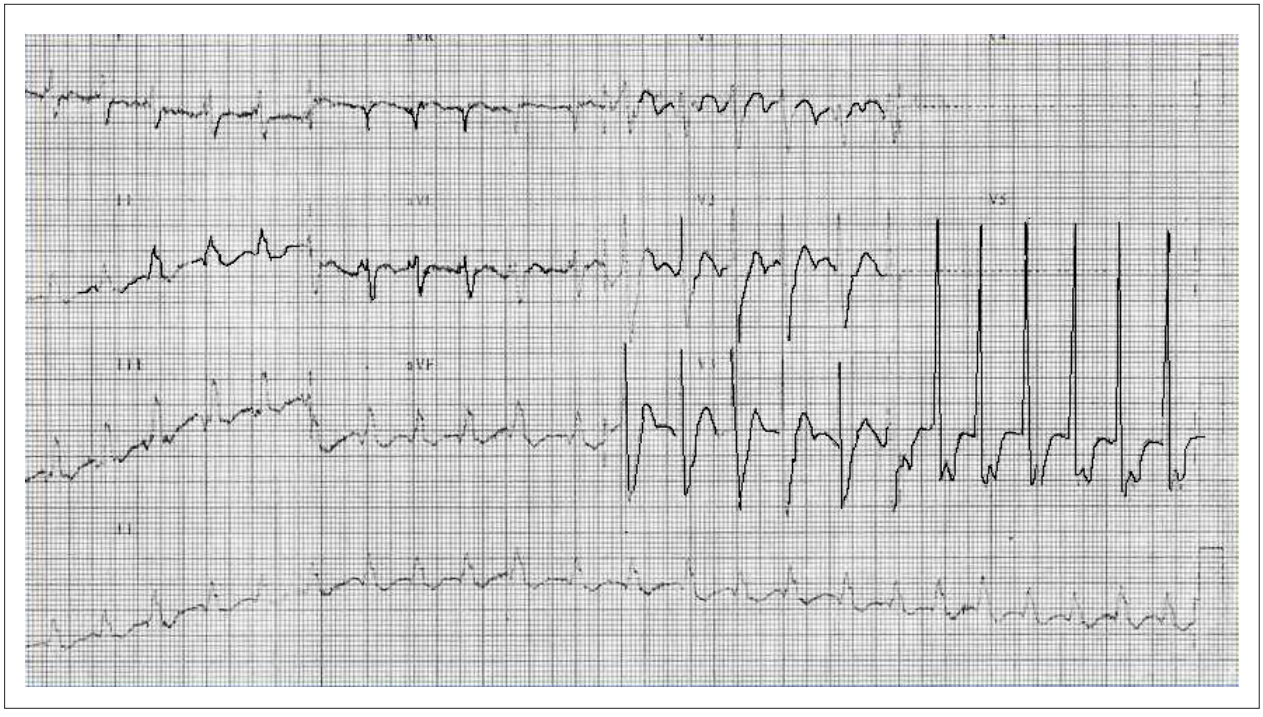

Figure 3 – *ECG: atrial fibrillation, intraventricular conduction disturbance and left ventricular overload.*

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in the other 50% it is asymmetrical and frequently affects the interventricular septum. HCMP may be classified as an obstructive or nonobstructive disease. Obstruction is defined in the presence of an intraventricular or LV outflow tract pressure gradient > 30 mmHg[3].

Clinically, HCMP manifests as a heart failure (HF) syndrome and/or as cardiac arrhythmias. In HF, ventricular diastolic dysfunction initially predominates, and loss of the systolic function is observed later in the natural progression of the disease. Both supraventricular and ventricular arrhythmias may occur in HCMP and their clinical manifestations range from symptomatic palpitations with or without decompensation of heart failure, syncope or sudden death. Sudden death is the most feared presentation of the disease, and is commonly the initial presentation of HCMP; it is the major cause of sudden death in individuals with up to 40 years of age[3,6].

The patient reported was a young woman who first presented with HF and palpitations at 30 years of age, when she was diagnosed with asymmetrical septal HCMP with preserved EF. In a subsequent assessment (with Looper recording) nodal reentrant tachycardia (NRT) was also identified; ablation via the slow nodal pathway was indicated, and successfully performed. Three years later, the patient had new episodes of palpitations; atrial fibrillation (AF) was detected and oral anticoagulation and amiodarone were started. After developing AF, the patient presented progressive worsening of symptoms of HF; ECHO showed progressive deterioration of the systolic ventricular function. Eight years after HCMP was diagnosed, the patient was admitted in the emergency room with acute pulmonary edema and AF with fast ventricular response, which complicated with pneumonia and resulted in death.

AF is a frequent complicating factor for these patients, both for the risk of cardioembolic events and of HF decompensation. As was done with the patient reported, oral anticoagulation should be indicated and AF should be controlled. If the patient already has permanent AF, control of the heart rate is fundamental[3,6].

Although patients with HCMP usually have symptoms of HF, only 10% to 15% of those with preserved ejection fraction progress to functional class III or IV, and only 3% develop significant ventricular systolic dysfunction. Factors associated with this progression are the presence of AF and LV outflow tract obstruction. Systolic dysfunction is a marker of very poor prognosis, with progression to refractory HF or sudden death by 10% per year[6].

Progression of disease as evidenced by the development of AF, worsening of HF symptoms and deterioration of LV ejection fraction in this patient pointed to a poor prognosis. Deterioration of the LV systolic function in patients with HCMP, even when minor, should be regarded as a warning sign of progression to irreversible end-stage disease. In these cases, in addition to optimized drug therapy for HF, early indication of cardiac transplantation should be considered.

Working diagnosis: hypertrophic cardiomyopathy progressing to dilatation and heart failure. **(Dr. Fernando Luiz de Melo Bernardi)**

Necropsy

The heart weighted 408 g. On external examination, pronounced dilatation of both atria and ventricles could be observed; their volume and shape were preserved. Cross-section of the ventricles showed irregular areas of replacement fibrosis in the myocardium that were exuberant in the left ventricular posterior wall, ventricular septum and right ventricular anterior wall (Figure 4). The left ventricular walls and ventricular septum had approximately the same thickness of approximately 1.0 cm. The right ventricular wall thickness was 0.3 cm. Histological examination of the ventricular myocardium confirmed the areas of replacement fibrosis seen on gross examination and revealed diffuse interstitial fibrosis, extensive areas of cardiomyocyte disarray (Figure 5), and focal areas of arterioles with markedly thickened walls (Figure 6). No thrombi were observed in the cardiac chambers, and gross examination of the epicardial coronary arteries did not show significant atherosclerosis or luminal obstruction. The lungs weighted 634 g taken together and showed chronic passive congestion with septal thickening and presence of hemosiderin-laden macrophages. No acute edema, pulmonary thromboembolism or bronchopneumonia were observed. Multiple areas of previous healed infarctions were found in the cortex of both kidneys, and a single small previous healed cortical infarction was found in the left occipital region of the brain. **(Dr. Luiz Alberto Benvenuti)**

Pathological diagnoses – Symmetrical hypertrophic cardiomyopathy; previous healed infarcts in the cortex of both kidneys and focal healed infarct in the brain; chronic passive pulmonary congestion **(Dr. Luiz Alberto Benvenuti)**

Comments

A 41-year-old female patient diagnosed with HCMP[7] and difficult-to-treat cardiac arrhythmias, who had in-hospital sudden death while awaiting cardioverter-defibrillator implantation. Necropsy confirmed the diagnosis of HCMP because of the presence of extensive areas of cardiomyocyte disarray, a typical finding of this disease. It is interesting to note that no asymmetry of the left ventricular walls was found and their thickness was within normal limits; thus the diagnosis of symmetrical HCMP[8] was made.

However, we should bear in mind that necropsy shows how the heart looks like at the moment of death with the changes secondary to cardiac remodeling that occurred throughout the disease, and that asymmetry in the initial phases of the heart disease cannot be ruled out, as suggested by the previous echocardiographic studies. The repeated tests also revealed progressive decrease of the left ventricular ejection fraction, thus confirming the development of progressive HF, which can occur in HCMP[7]. We should also point out the presence of extensive areas of replacement fibrosis in the ventricular myocardium that were irregular and located in both ventricles, and which we believe were the arrhythmogenic morphological substrate. The occurrence of areas of ventricular fibrosis is described in HCMP and seems to correlate with the presence of changes in the coronary microcirculation, such as those reported in the present case, with significant arteriolar wall thickening[8].

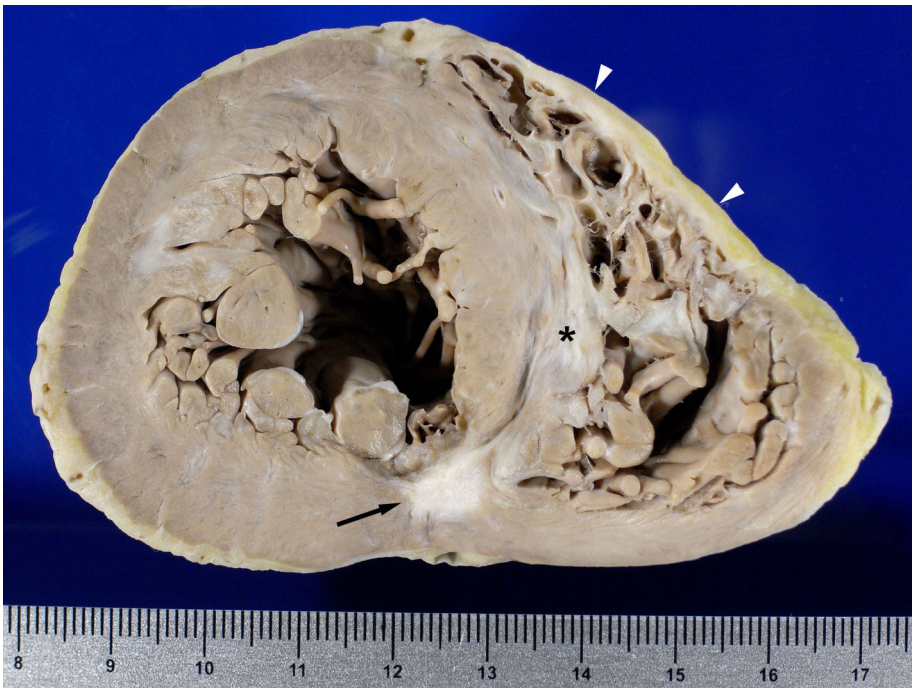

Figure 4 – *Cross-section of ventricles showing irregular areas of fibrosis, especially in the left ventricular posterior wall (arrow), ventricular septum (asterisk) and right ventricular anterior wall (arrowheads). Note that there is no significant asymmetry of the left ventricular walls, whose thickness is within normal limits.*

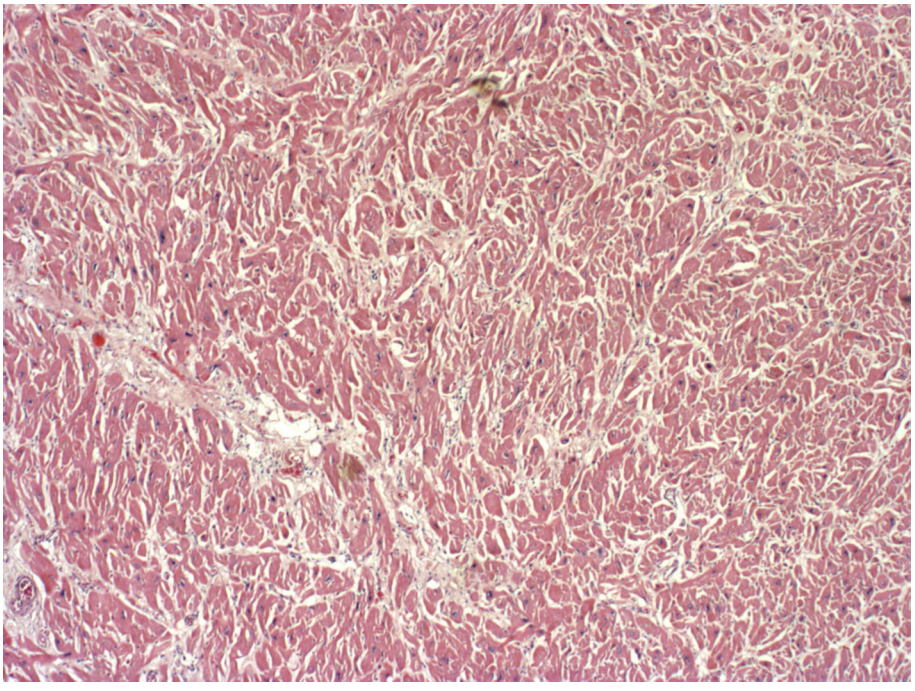

Figure 5 – *Histological section of left ventricular myocardium showing cardiomyocyte disarray. Hematoxylin-eosin staining, X 25.*

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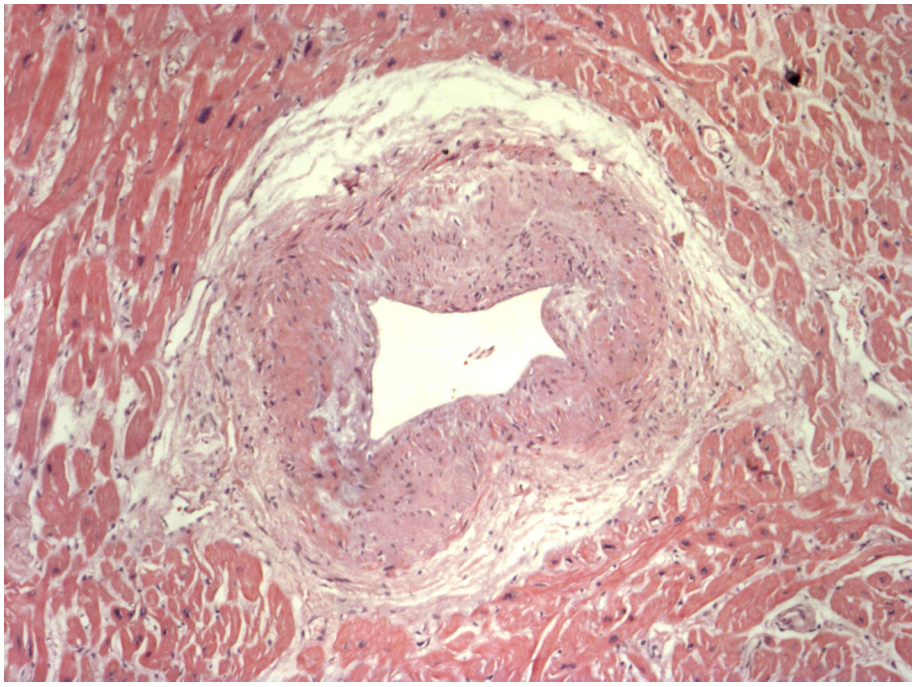

Figure 6 – *Arteriole of the left ventricular myocardium showing significant wall thickening due to hypertrophy of the muscular layer. Hematoxylin –eosin staining, X 50.*

Although thrombi were not found in the cardiac chambers on necropsy, it is very likely that systemic thromboembolism from this site had occurred; this is corroborated by the occurrence of atrial fibrillation, history of thromboembolectomy of a left upper limb artery, and the necroscopic findings of areas of healed infarction in the kidneys and brain[9].

We believe that the sudden death resulted from cardiac arrhythmia, because we did not find any other cause such as acute pulmonary edema or pulmonary thromboembolism that could explain it. Sudden death for cardiac arrhythmia is an event described in HCMP[10]. **(Dr. Luiz Alberto Benvenuti)**

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