Case 5/2010 - A 41 Year-old Man with Myocardial Hypertrophy who Evolved with Congestive Heart Failure

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A 41-year-old man from the city of São Paulo sought medical attention due to rapidly progressive dyspnea and generalized edema. The patient was aware of having arterial hypertension and left ventricular hypertrophy.

The patient had remained asymptomatic until 33 years old when he started to present exertional dyspnea. He sought medical attention at the time and was diagnosed with enlarged cardiac area. The clinical picture remained stable until he was 35 years old (May 2001), when he presented an episode of tachycardic palpitations and precordial pain. He sought medical attention and atrial flutter was diagnosed. The echocardiogram (September 13, 2001) disclosed moderate left ventricular hypertrophy (LVH) and pericardial effusion; the coronary angiography (October 18, 2001) did not show coronary artery obstructions. He was prescribed amiodarone and was referred to our hospital.

At physical examination (December 13, 2001), the patient presented heart rate (HR) of 68 bpm, blood pressure (BP) of 140/95 mmHg. The remainder of the physical examination did not show any other alterations or diagnostic findings.

The electrocardiogram (December 18, 2001) disclosed sinus rhythm, HR of 78 bpm, duration of PR = 157 ms, QRS = 108 ms, QT = 414 ms, SÂQRS + 130° shifted backward. The morphological analysis disclosed an increased P wave, QS in leads I, aVL and Q wave in lead V6. Right atrial overload, electrically inactive lateral area and ventricular repolarization alterations were diagnosed.

Laboratory assessment (December 19, 2001) disclosed: hemoglobin - 15.5 g/dl; hematocrit - 46%; total cholesterol - 242 mg/dl; triglycerides - 241 mg/dl; fasting glycemia - 107 mg/dl and creatinine - 1.3 mg/dl.

Keywords

Heart failure; hypertrophy, left ventricular; hypertension; atrial fibrillation; amyloidosis.

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Treatment with amiodarone was withdrawn and atenolol was prescribed.

The patient started to present worsening of exertional dyspnea. The worsening was associated with the use of atenolol, which was discontinued, and the patient restarted amiodarone, 200 mg/day.

The patient was submitted to ergometric test (February 21, 2003). At basal condition, the HR was 124 bpm and BP was 134/98 mmHg; after 2 minutes and 45 seconds of exertion, these parameters were 192 bpm and 158/94 mmHg. He started to present atrial fibrillation and nonsustained ventricular tachycardia during exertion.

The Holter ECG recording (February 21, 2003) disclosed rhythm of atrial fibrillation, 202 isolated ventricular extrasystoles and an episode of nonsustained ventricular tachycardia with 4 beats and HR of 155 bpm.

The echocardiogram (2003) disclosed enlarged left and right atria, asymmetric septal hypertrophy and normal left ventricular ejection fraction (LVEF) (Table 1).

Enalapril (5 mg), amiodarone (200 mg) and warfarin (5 mg) were prescribed.

The symptoms abated; the exertional dyspnea persisted, as well as occasional episodes of palpitations, throughout two years. Subsequently, the dyspnea presented rapid increase, which started to occur even with the patient at rest. After one month, the patient had not improved and sought medical attention.

At physical examination (June 3, 2004), the patient presented HR of 98 bpm, 24 breaths per minute, BP of 140/110 mmHg, increased jugular venous pressure, rales in the left hemithorax. Heart assessment disclosed arrhythmic beats, muffled heart sounds and systolic murmur +++/4+ in the aortic area. The liver was palpable at 2 cm from the right costal margin and the patient presented ++/4+ lower-limb edema.

The chest X-ray showed an enlarged cardiac area with a round shape.

The electrocardiogram (June 5, 2004) showed atrial flutter, HR of 79 bpm, low voltage of the QRS complex in the frontal plane, QRS axis shifted to the right and forward and decrease of the left ventricular potentials, suggesting right ventricular overload and an electrically inactive area in the lateral wall (Figure 1).

The echocardiogram (June 3, 2004) showed that the dimensions of the left ventricle (LV) and left atrium (LA)

Figure 1 - ECG: atrial flutter and probable right ventricular overload (right-shifted and anteriorized SÂQRS).

were similar to the previously measured ones, in addition to right ventricle (RV) hypertrophy and large pericardial effusion, without signs of cardiac restriction or cardiac tamponade (Table 1).

Pericardial drainage and biopsy were indicated. At the intervention (June 5, 2004), 450 ml of citrine-yellow fluid was drained. The anatomopathological analysis of the pericardial fragments disclosed slight fibrosis and neovascularization of the pericardium, with no evidence of neoplastic cells or inflammatory infiltrate.

The control echocardiogram (June 15, 2004) disclosed slight pericardial effusion. The patient presented improvement

of the dyspnea and was discharged from the hospital (June 15, 2004).

The mapping of the myocardial thickness by echocardiogram (June 4, 2007) disclosed the following measurements: anterior (basal 17 mm, mean 19 mm), anteroseptal (basal 20 mm, mean 22 mm), inferoseptal (basal 15 mm, mean 16 mm), inferior (basal and mean 11 mm) and inferolateral (basal 12, mean 13 mm), anterolateral (basal 11 mm, mean 15 mm), apical-septal 14 mm, apical-lateral 14 mm, apical cap 12 mm. The high-resolution electrocardiogram (July 26, 2007) disclosed QRS enlargement - standard QRS duration: 140 ms; filtered QRS duration: 130 ms; duration < 40 mV 14 ms; and absence of low-amplitude late potentials in the final 40 ms, 61,7 mV.

The dyspnea at moderate exertion remained stable for 4 more years, until it progressed to dyspnea at rest in the decubitus position in May 2008, along with generalized edema. After twenty days, as there was no improvement, the patient once again sought medical attention (June 6, 2006).

At physical examination (June 6, 2008), the patient showed regular general status, with a pulse rate of 90 bpm and BP of 70/50 mmHg. The jugular venous pressure was high. Pulmonary assessment was normal. Heart assessment showed muffled heart sounds and no murmurs. The abdomen was globular and the patient presented ascites, in addition to ++++/4+scrotal and lower-limb edema.

The ECG (June 6, 08) disclosed atrial fibrillation, HR of 96 bpm, QRS duration of 143 ms, low-voltage QRS complex, SÂQRS + 130 forward, right bundle-branch block, with pure R wave in V1 and V2, and electrically inactive lateral area (Figure 2). The chest X-ray (June 6, 2008) disclosed

Table 1 - Echocardiographic evolution

	2003	2004	2007	11 June 08
Aorta (mm)		26		32
Left atrium (mm)	58	58	62	59
Septum (mm)	23	19	20	22
Posterior wall (mm).	12	13	12	12
LV				
Diastole (mm)	37	40	42	38
Systole (mm)	25	30	29	29
LVEF (%)	68		56	48
RV systolic pressure (mmHg).		60		
RV (mm)		40	Dilated	Dilated

LV - left ventricle; RV - right ventricle; LVEF - left ventricular ejection fraction.

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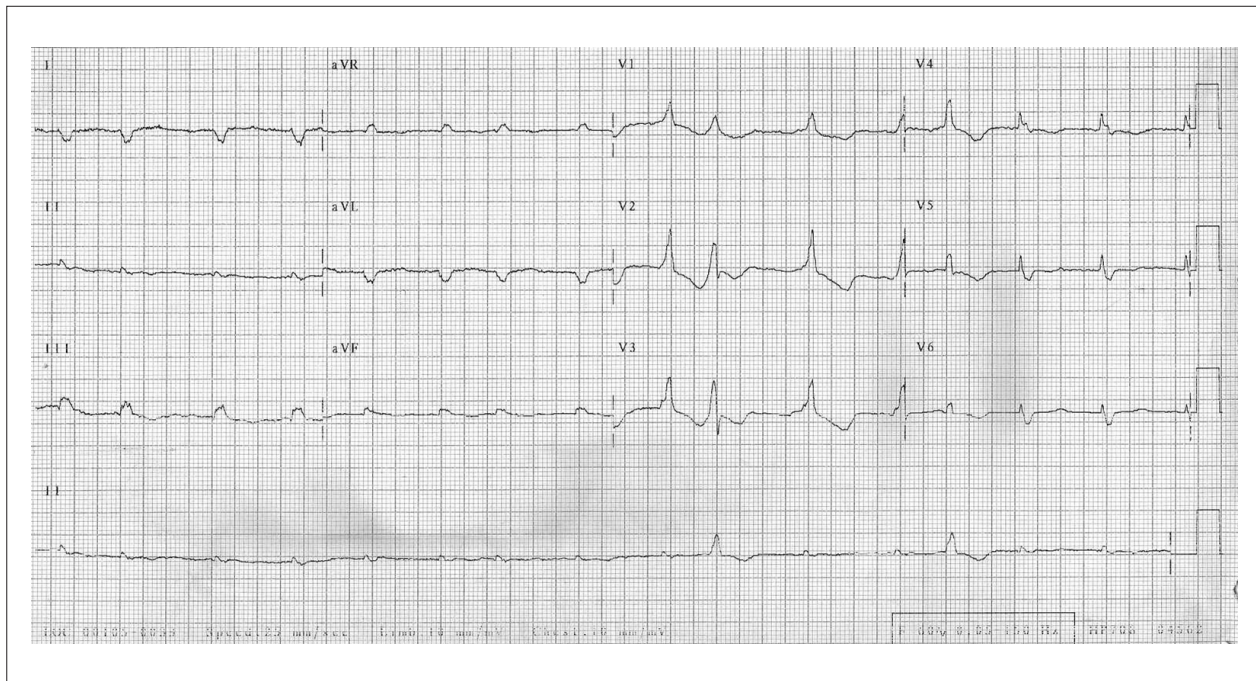
Figure 2 - ECG: atrial fibrillation, low-voltage frontal plane, enlarged QRS, pure R wave in V_1 and V_2.

global enlargement of the cardiac area, with no signs of pulmonary congestion.

The laboratory assessment (June 6, 08) showed hemoglobin=11.5 g/dl, hematocrit 34%, leukocytes 6,700/mm^3 (68% neutrophils, 1% eosinophils, 1% basophils, 13% lymphocytes and 17% monocytes), platelets = 161,000/mm^3, urea = 67 mg/dl, creatinine = 2.3 mg/dl, potassium = 3.6 mEq/l, sodium = 136 mEq/l, INR prothrombin time = 2.7, activated prothrombin time ratio 1.57, MB-fraction creatine phosphokinase = 3.73 ng/ml and troponin I = 0.21 ng/ml.

The echocardiogram (June 11, 08) showed LV and RV hypokinesia and marked tricuspid regurgitation and moderate pericardial effusion (Table 1).

The total abdominal ultrasonography (US) (June 12, 08) showed no abnormalities in the urinary system, inferior vena cava and hepatic vein ectasia, moderate ascites, blunt liver edge and finely heterogeneous texture.

The laboratory assessment (June 12, 2008) showed creatinine 2.94 mg/dl, urea 110 mg/dl, potassium 5.9 mEq/l, sodium 134 mEq/l.

The ventilation and pulmonary perfusion scintigraphy (June 16, 2008) was considered as being low-probability for pulmonary thromboembolism.

The cardiac scintigraphy with technetium pyrophosphate (June 20, 2008) showed slight to moderate diffuse uptake in the myocardium (Figures 3 and 4).

The cardiac magnetic resonance (June 27, 2006) showed marked biatrial dilatation; ventricular chambers with normal dimensions; slightmild left ventricular dysfunction due to diffuse hypokinesis; normal right ventricular function. There was marked tricuspid regurgitation and moderate pericardial
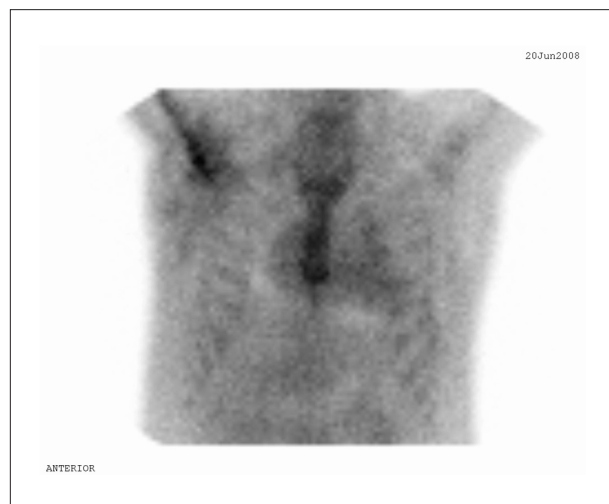
Figure 3 - Technetium pyrophosphate scan, anterior view: pyrophosphate uptake in the cardiac area, in addition to more intense uptake in the sternum.

effusion, bilateral pleural effusion and no thrombi. The findings were considered compatible with amyloidosis.

The screening for Bence Jones protein in urine was negative.

During patient evolution, the echocardiogram (July 11, 08) disclosed marked pericardial effusion (Table 1).

In spite of the treatment with diuretics and inotropic drugs by IV route, the patient presented marked worsening in the clinical picture, with generalized edema, pleural effusion and pericardial effusion. A pericardial drainage was carried out, in addition to bilateral paracentesis thoracis, without
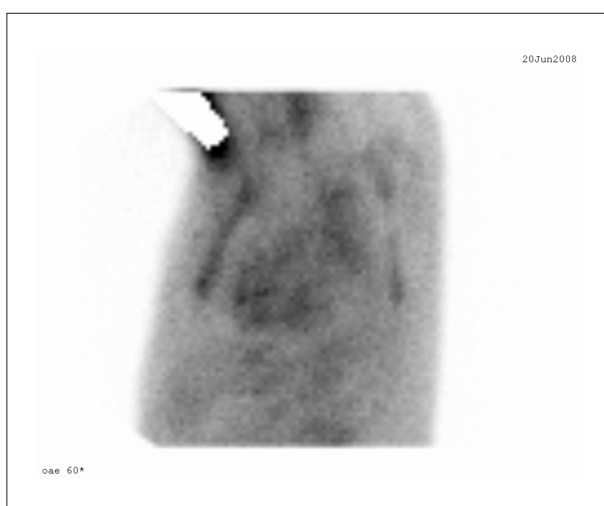
Figure 4 - Technetium pyrophosphate scan, left anterior oblique view at 60°: pyrophosphate uptake in the cardiac area, in addition to more intense uptake in the sternum.

complications (July 18, 2008).

The patient presented coughing with purulent expectoration. Gram negative cocci were identified in the left pleural fluid. Antibiotic therapy with oxacillin and ceftriaxone (July 21, 2008) was started and subsequently substituted by tazobactam and vancomycin. The total abdominal US (July 22, 2008) disclosed hepatomegaly with normal shape and borders and blunt edges; the intra and extra-hepatic bile ducts were normal and the patient presented homogenous splenomegaly; moderate ascites was present. The kidneys were normal.

The laboratory assessment (July 26, 2008) showed hemoglobin = 10.5 g/dl, hematocrit = 33%, leukocytes = 36,400/mm^3 (3% promyelocytes, 2% myelocytes, 8% metamyelocytes, 9% band cells, 63% segmented, 2% eosinophils, 1% basophils, 3% lymphocytes and 9% monocytes), platelets = 102,000/mm^3, urea = 77 mg/dl, creatinine = 3 mg/dl, bilirubin = 7.8 mg/dl (direct = 6.6 mg/dl), alkaline phosphatase = 107 UI/l, gamma GT = 215 UI/l, aspartate aminotransferase = 47 UI/ml, alanine aminotransferase = 45 UI/l, C-reactive protein = 163 mg/l, arterial lactate = 52 mg/dl, prothrombin time (INR) = 2.1, TTPA ratio =1.5, arterial gasometry: pH 7.20, pCO$_2$ 39.5 mmHg, pO$_2$ 75.7 mmHg, O$_2$ saturation = 92.5%, bicarbonate = 14.8 mEq/l and base excess = -12.1mEq/l.

In spite of the therapeutic measures, the patient developed septic shock staring on July 23, 2008; multiple organ failure ensued and the patient died due to asystole (July 27, 2008).

Clinical aspects

The patient, at the initial clinical picture at 33 years, complained of exertional dyspnea. At that time, it was important to try to define the most probable origin of the complaint. When it is the result of cardiopathy, dyspnea is associated with the increase in pulmonary capillary pressure, with consequent secondary interstitial congestion. Other potential causes of dyspnea can be pulmonary and thyroid

causes, anemia, etc[1,2]. The presence of cardiac enlargement at the chest x-ray increaseds, at thatis moment, the probability of cardiac origin.

Therefore, this is a patient with heart failure (HF), which could be caused by left ventricular systolic (LV ejection fraction [LVEF] < 50%) or diastolic dysfunction (abnormal difficulty in LV diastolic filling)[3].

Diastolic dysfunction is the cause of HF in 40 to 50% of the patients. The diagnosis of HF with preserved EF (HFPEF) and diastolic dysfunction is established with the simultaneous presence of three factors: signs or symptoms of congestive HF; normal or slightly decreased LVEF; and objective evidence of LV diastolic dysfunction: abnormal LV relaxation and filling, abnormal diastolic distensibility or diastolic stiffness. The evidence of diastolic dysfunction can be obtained from hemodynamic data, natriuretic peptide levels, echocardiographic and tissue Doppler data[4].

The evolution with precordial pain and palpitations after two years, without significant alterations at the physical examination, with ventricular hypertrophy and normal EF at the echocardiogram, in addition to the pericardial effusion and absence of coronary disease, raises the possibility of hypertensive heart disease, myocarditis accompanied by pericardial involvement, hypertrophic cardiomyopathy (HCM) and restrictive syndromes, such as deposition diseases.

The hypertensive heart disease can be defined as the result of the LV overload caused by the increase in BP and total peripheral vascular resistance. In this case, this is a young patient with LV hypertrophy (LVH) that developed HFPEF. As a consequence of the LVH, one can observe the increased incidence of some arrhythmias, such as ventricular extrasystoles, complex ventricular arrhythmias[5] and atrial fibrillation (AF), which would justify the tachyarrhythmias presented by the patient.

The electrocardiogram (ECG), for the diagnosis of LVH, is a method with little sensitivity, albeit highly specific; however, the findings of the patient discussed herein do not meet these criteria. As for the echocardiogram, it is a low-cost method and considered the noninvasive method of choice for the diagnosis of increased cardiac mass. One could consider investigating secondary hypertension, as this was a young patient with LVH. However, in this case, as the patient apparently achieved BP control using only 5 mg of enalapril, thus attaining easy BPO control, as well as taking into account the patient evolution and the fact that the hypertrophy was clearly asymmetric, the hypothesis of hypertensive heart disease should be ruled out[6,7].

The myocardites, which are more often caused by viral agents[8], present a broad spectrum of clinical presentation, which varies from subclinical or oligosymptomatic pictures to sudden cardiac death. Infection by some specific agents might be associated with less frequent presentations, such as the phenotype of hypertrophic cardiomyopathy without ventricular dysfunction - initially presented by this patient - which can be caused the hepatitis C virus, with a higher prevalence among Asian country populations[9]. Additionally, in fulminant myocarditis, characterized by a very severe acute presentation that includes cardiogenic shock, the echocardiographic assessment discloses an increase in the septal thickness with a lower increase in the ventricular diameters.

The presence of arrhythmias associated with myocardial alterations is also frequent in myocardites and very often necessitates specific treatment, and/or being an indicator of possible unfavorable disease evolution, as in giant-cell myocarditis. In this specific type of myocardial inflammation, however, a shorter-duration history would be expected - differently from the present case - as the patients present poor prognosis, with a mean survival of less than 6 months and very frequent need for heart transplant when they survive the acute phase[8].

The active chronic myocarditis, in turn, would characteristically present a longer and more insidious evolution, usually with a phenotypic manifestation of dilated cardiomyopathy, with mortality rates that are as high as 56% in four years. Pericardial involvement can also occur, associated with the myocardites[8].

Another hypothesis for the case would be restrictive and infiltrative cardiomyopathies, which are characterized by limitation in ventricular filling and ventricular stiffness, with normal or slightly dilated ventricles and significant atrial dilatation[9]. Ventricular thickness is normal or increased, depending on the etiology. The symptoms can be caused by RV failure, which manifests with increased jugular venous pressure, peripheral edema and ascites and/or LV failure, causing dyspnea and pulmonary edema[10,11]. The restrictive cardiomyopathy is the rarest of all cardiomyopathies and amyloidosis is its most common form[12].

One of the causes of restrictive cardiomyopathy, sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by the involvement of several tissues by non-caseous granulomas[13]. The primary cardiac involvement is rare and the clinical manifestations appear in less than 5% of the patients and are characterized by conduction disorders, ventricular arrhythmias, syncope and sudden death. The direct myocardial involvement by the granulomas and scar tissue can manifest as dilated or restrictive cardiomyopathy, with a progressive course[14,15]. The ECG is nonspecific and can present T wave abnormalities, blockades or pathological Q waves. Other findings include pericarditis and cor pulmonale.

The echocardiogram can disclose ventricular wall thinning and increased echogenicity[14,16]. The cardiac magnetic resonance (CMR) is a highly sensitive and specific method for its diagnosis. The case presented herein showed only cardiac involvement, without the other manifestations of the disease and the CMR did not disclose suggestive alterations, which makes this diagnosis unlikely[17].

Fabry's disease is an X-linked recessive disorder that results from the deficiency of the lysosomal enzyme alpha-galactosidase A. In its classic form, it is characterized by marked skin, kidney and myocardial involvement, including the manifestation of angina pectoris and myocardial infarction, although in most cases the coronary arteries have normal angiographic aspect. There is an increase in the LV thickness, with preserved systolic function and slight diastolic dysfunction and mitral regurgitation. The CMR is adequate to differentiate Fabry's disease from other cardiomyopathies[10,11]. The present case did not present extracardiac manifestations compatible with the disease and the CMR result was suggestive of another disease.

Hemochromatosis results from the deposition of iron in parenchymatous tissues, such as heart, liver, gonads and pancreas. Its classic presentation is the onset of heart failure, liver cirrhosis, erectile dysfunction, diabetes mellitus and arthritis. The cardiac involvement leads to a combined pattern of dilated cardiomyopathy and restrictive cardiomyopathy with systolic and diastolic dysfunctions. The ECG shows ST-segment and T-wave alterations and supraventricular arrhythmias.

The echocardiogram shows ventricular wall thickening, dilatation and dysfunction. The markers of iron kinetics are altered[10,11]. The T*2 CMR acquisition technique can establish the diagnosis[18].

The present case did not present suggestive extracardiac manifestations and the complementary examinations were not compatible with hemochromatosis.

The endomyocardial diseases manifest with endocardial fibrosis that obliterates the ventricular apex and subvalvular regions[10,11]. As observed, this is not the pattern verified in the present case.

Amyloidosis is a deposition disease that can be classified according to the biochemical nature of the amyloid protein as primary, secondary, senile, familial amyloidosis and amyloidosis of patients with dialytic renal failure. It must be considered as a differential diagnosis in any patient older than 40 years with unexplained heart failure, nephrotic syndrome, peripheral neuropathy or hepatopathy. Secondary amyloidosis and the amyloidosis of chronic kidney patients rarely present cardiac involvement. The ECG shows atrioventricular blocks and low-voltage QRS complexes and the high-resolution ECG is valuable in predicting the risk of sudden death, differently from what occurs in cases of HCM. Similarly to this other disease, however, amyloid infiltration can also predispose to AF and ventricular arrhythmias[10,11,19,20].

The echocardiogram shows an increase in myocardial thickness, which has a granular aspect, atrial dilatation, pericardial and/or pleural effusion and diastolic dysfunction. The pericardial effusion does not usually develop into cardiac tamponade and the presence of RV dysfunction is an independent predictor of poor prognosis[10,11]. The 99mTechnetium pyrophosphate scintigraphy shows uptake proportional to the intensity of the amyloid deposition[11]. As this radionuclide is capable of binding to the calcium, the examination can be altered in other situations as well, such as calcifications and other deposition diseases. The CMR has high sensitivity and specificity that can vary from 75% to 94%, when a pattern characterized by global and heterogeneous subendocardial late enhancement with gadolinium is found[17,21,22], whereas the biopsy characterizes the amyloid substance and confirms the suspected amyloidosis.

In the present case, initially, the diagnosis of amyloidosis seemed unlikely due to the patient's age and the ECG results. However, during the case evolution, the change in the electrocardiographic pattern was closer to the one commonly seen in cases of amyloidosis (low voltage); nevertheless, it was not possible to establish whether that occurred solely due to the pericardial effusion. Moreover, the screening for Bence Jones protein was negative. On the other hand, the patient presented severe restrictive syndrome and a pyrophosphate

scintigraphy and CMR were performed, which are compatible with this diagnosis. Therefore, it would be possible to consider cardiac amyloidosis, in its primary form, as the diagnosis of the present case.

A differential diagnosis of restrictive cardiomyopathy is constrictive pericarditis, characterized by pericardial fibrosis that prevents the filling of the cardiac chambers. Systemic venous congestion occurs, as well as a decrease in the cardiac index. The ECG normally shows unspecific alterations in the T wave and decreased voltage, in addition to signs of left atrial overload or AF. The chest X-ray shows right atrial enlargement and the echocardiogram can disclose pericardial calcifications and pericardial effusion. However the present case showed increased ventricular wall thickness, pulmonary artery systolic pressure > 50 mmHg and no pericardial thickening at the CMR, all suggestive of restrictive, not constrictive, syndrome[10,11].

Finally, the HCM constitutes the genetic heart disease with the highest prevalence[23] and the most common cause of sudden death in young people[24]. An asymmetric pattern of hypertrophy is characteristic of the disease and 70% to 75% of the cases present echocardiographic evidence of diffuse hypertrophy of the ventricular septum and the anterolateral wall, as well as a description of right ventricular hypertrophy in some patients[25]. The clinical manifestations can appear at any age, with the diagnosis being more frequent during adolescence and the start of adult life.

The disarray of the myocardial structure induced by the disease, associated with the increase in the ventricular mass and the alterations present in the coronary microvasculature lead to silent myocardial ischemia, with the formation of areas of fibrosis that can correspond to electrically unstable regions, from which ventricular arrhythmias can originate. Additionally, these areas of fibrosis, associated with regional hypertrophy (generally, septal), can lead to ECG alterations with atrial overload, for instance, R waves in V1, decrease in R waves and appearance of Q waves in lateral wall leads (DI, aVL, V5 and V6), alterations in ventricular repolarization and, in cases of lateral-wall fibrosis, rightward shift of axis, as it can be observed in the present case. During disease evolution, QRS enlargement can also occur, which is compatible with the present case[26].

The patients can present LV outflow tract obstruction, which is related to the development of HF clinical picture, a higher rate of cardiovascular death and a higher risk of sudden death[3], which can be reduced with the use of beta-blockers and increased, among other situations, in the presence of ventricular extrasystoles (VE) and in Valsalva maneuver.

The patient presented clinical worsening after the withdrawal of amiodarone and the start of atenolol use. If the diagnosis of HCM had been correct and therefore, the use of beta-blocker had been correctly indicated, the amiodarone withdrawal might have been associated with an increase in the VE frequency, with a consequent increase in the subaortic gradient, which might have led to the onset of an obstructive component in the disease, thus generating the worsening in the dyspnea symptom. Another possible cause of the worsening with amiodarone withdrawal might have been the higher incidence of supraventricular paroxysmal arrhythmias, such

as AF, known to be associated with the clinical worsening in these patients, with a worse prognosis[23,26]. It is known that the incidence of supraventricular arrhythmias, including AF, in Holter recordings can be as high as 30% in adults[26]. The presence of AF in this population, even at the first or the second paroxysmal episode, is capable of generating thrombus formation and cardioembolic phenomena, resulting in the indication of anticoagulation for these patients, with a low threshold for its start[24,27].

Ten to 15% of the patients develop limiting heart failure (New York Heart Association functional class III or IV), and only 3% manifest advanced disease with LVEF < 50%[28]. A study published in 2007 showed that, among 1,226 patients with a diagnosis of HCM, the prevalence of the restrictive phenotype was 1.5%[29].

The patients with the studied phenotype presented higher diastolic dysfunction and higher left atrial diameter, in addition to lower tolerance to exercise and worse prognosis, with a 5-year survival of 56% – versus 90% in those without the restrictive phenotype (p=0.008) – with 42% of the cases presenting signs of right heart failure, such as ascites, abdominal discomfort and edema. There was also a higher tendency to the development of AF or atrial flutter and higher rates of cerebrovascular accident. It can be observed that during disease evolution, the patient described herein presented several characteristics that were compatible with this disease phenotype.

Due to the possibility of sudden death, previous studies have defined risk markers, used in the stratification of these patients. Those diagnosed before 14 years of age present a higher risk. Other factors include: personal history of syncope or reverted sudden death; severe hypertrophy (> 30 mm)[30]; presence of non-sustained ventricular tachycardia (NSVT) at Holter monitoring; abnormal BP behavior at exertion - decrease in BP or increase < 25 mmHg in the systolic pressure[26]. The high-resolution ECG, the analysis of the QT interval dispersion and of the heart rate variability present low predictive acuracy[31]. In the present case, the patient presented, among the listed risk factors, NSVT at Holter monitoring and did not present a BP curve that could be assessed at the ergometric test, considering the low workload.

The clinical picture presented a progressive feature since the diagnosis, characterized by three important decompensation episodes, with increasingly more significant clinical, electrocardiographic and echocardiographic alterations. At the last hospital admission, the patient developed a biventricular systolic dysfunction, marked pericardial effusion, edema, ascites and cardiogenic shock, accompanied by kidney failure, coagulopathy and pulmonary infection complicated by septic shock, which resulted in the patient's death.

Considering the age at the initial presentation, the clinical alterations observed throughout the years of evolution, the alterations at the complementary examinations and the characteristics of each one of the diseases presented during this discussion, we consider HCM as the main diagnostic hypothesis in the present case.

Dr. Rafael Moura de Almeida
and Dr. Lucas José Tachotti Pires

Anatomopathological Session

Diagnostic hypothesis

Restrictive syndrome secondary to hypertrophic cardiomyopathy.

**Dr. Rafael Moura de Almeida
and Dr. Lucas José Tachotti Pires**

Scintigraphy

Scintigraphy with 99mTc-pyrophosphate was performed on June 20, 2008 (Figures 3 and 4). The chest scintigraphy images, performed 3 hours after the IV administration of 99mTc-pyrophosphate, obtained on the anterior view (Figure 3) and left anterior oblique view at 60° demonstrate slight/moderate diffuse cardiac uptake.

The 99mTc-pyrophosphate binds to intracellular calcium, which accumulates in the cells due to sarcolemma alterations. It is worth mentioning that the normal myocardium does not present 99mTc-pyrophosphate uptake. This examination was frequently used in the past to evaluate acute myocardial infarction, where the classic pattern is that of focal uptake in the affected wall. The diffuse uptake is a rare and little specific finding, generally related to diseases that affect the heart diffusely, such as amyloidosis, sarcoidosis, perimyocarditis, endocarditis or subendocardial infarction. In amyloidosis, the degree of uptake is related to the degree of myocardial thickening, thus with prognostic implications[32,33]. In the present case, the diffuse uptake in hypertrophic cardiomyopathy is not expected and might be related to the findings of the necropsy of subendocardial infarction and/or pericarditis.

**Dr. José Soares Junior, Dr. Wilson Ichiki
and Dr. Wilson André Ichiki**

Necropsy

Approximately 250 ml of blood, as well as blood clots, leaked out at the opening of the pericardial sac. Diffuse fibrinous pericarditis was observed. The heart weighed 510 g (normal: 300-350 g) and presented increased volume of the four cardiac chambers. There was moderate dilatation of the right ventricle and of the atria. The ventricles presented moderate and symmetric hypertrophy, in relation to the thickness of the ventricular septum and the LV free wall = 1.2, without cavitary obstruction. There were extensive areas of fibrosis in the LV myocardium (Figures 5 and 6). The endocardium of both ventricles was narrow, smooth and shiny. The right auricle exhibited a small mixed thrombus, in the process of formation. No abnormalities were observed in the atrioventricular or ventricular-arterial valves. The study of the coronary arteries showed an intramyocardial trajectory ("myocardial bridge") from the 2nd to the 4th cm of the left interventricular branch (Figure 7) and the histological analysis showed mild coronary atherosclerosis, with a maximum 30% of obstruction of the lumen of the main coronary arteries.

Histological sections of the ventricles showed diffuse myocardial hypertrophy, spatial disarray of cardiomyocytes and of the cardiac fiber bundles in more than 20% of the sampled areas, diffuse interstitial fibrosis from the subendocardial to the subepicardial region and intramural coronary artery wall thickening due to intima-media proliferation of smooth muscle cells (Figure 8). Although present in both ventricles, these alterations were more marked in the ventricular septum and the LV free wall. The histochemical analysis for the presence of amyloid substance and glycogen in the myocardium were negative. Considering the anatomopathological findings of the necropsy, a diagnosis of restrictive hypertrophic cardiomyopathy, without cavitary obstruction, was attained. Chronic passive lung, liver and spleen congestion was also observed, as well as generalized subcutaneous tissue edema, consequent to congestive heart failure.
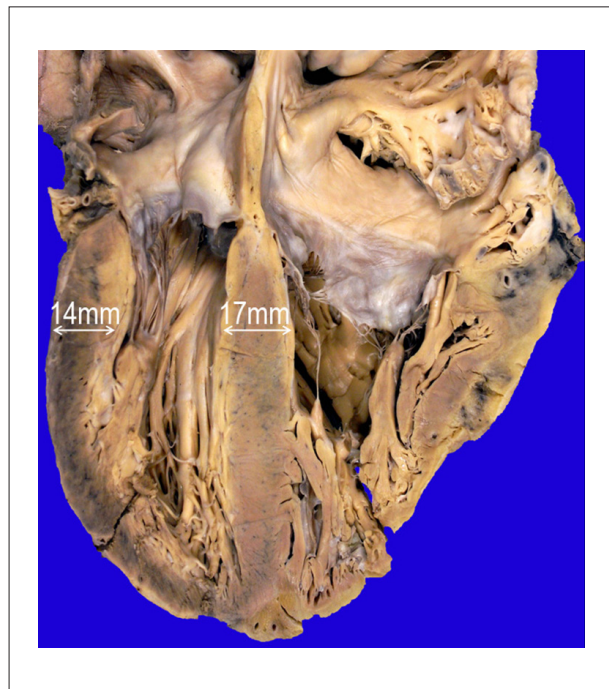
Figure 5 - Four-chamber view of the heart: symmetric hypertrophy of the left and right ventricles, without cavitary obstruction. Ratio between the ventricular septum/LV free lateral wall = 17 mm/14 mm = 1.2.
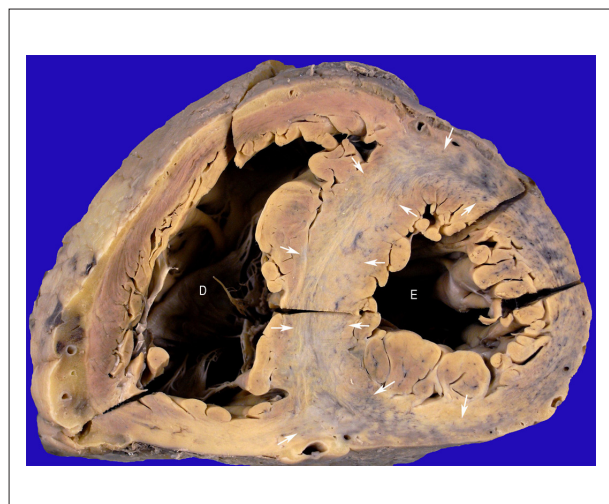
Figure 6 - Cross-section of the ventricles: myocardial hypertrophy of the left and right ventricles and marked fibrosis of LV myocardium (between arrows).
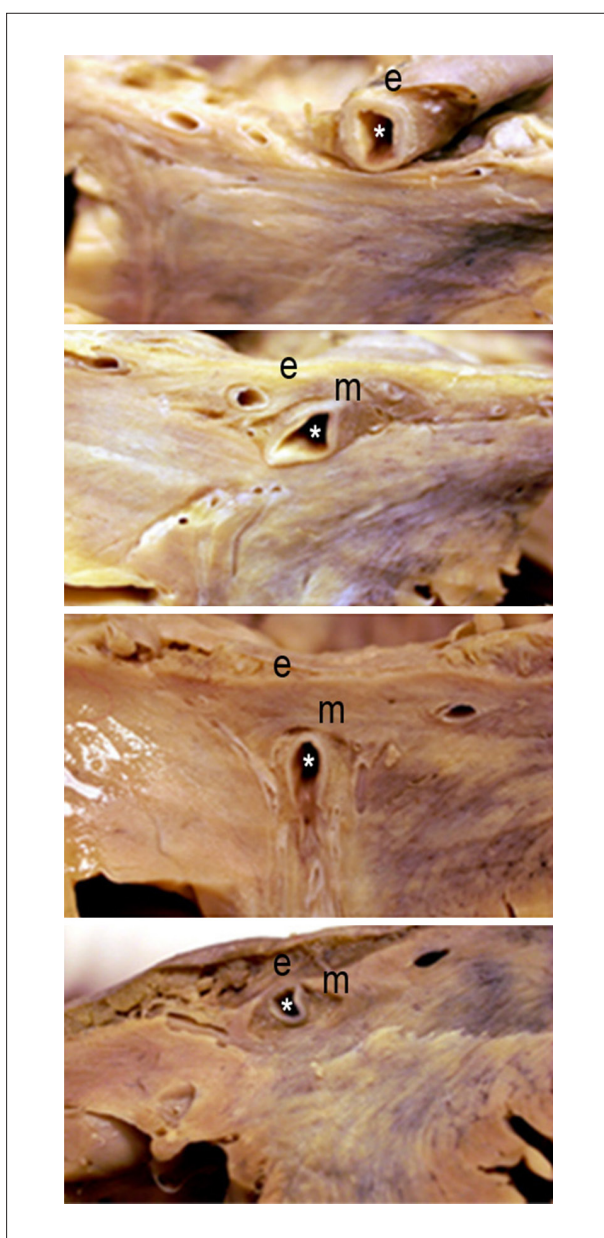
*Figure 7 - Cross-section of the ventricles: intramyocardial trajectory of the anterior interventricular branch of the left coronary artery (e - endocardium; m - myocardium; * - coronary lumen).*

The other organs showed alterations secondary to shock, represented by diffuse alveolar injury and intra-alveolar hemorrhage in the lungs, acute tubular necrosis in the kidneys, centrilobular liver necrosis and recent, small and multifocal subendocardial infarctions.

The lungs presented localized areas of bronchopneumonia at the initial stage. However, no morphological alterations suggestive of infection were observed in other organs. The presence of blood and blood clots in the pericardial sac seems to be one more final event, the result of the resuscitation maneuvers.

The cause of death was multiple-organ failure due to

shock, predominantly cardiogenic shock and aggravated by the pulmonary infection.

Dr. Léa Maria Macruz Ferreira Demarchi

Anatomopathological diagnoses

1) Symmetric and non-obstructive hypertrophic cardiomyopathy, on-ce; 2) Congestive heart failure; 3) Mixed (cardiogenic/septic) shock; 4) Multiple-organ failure.

Dr. Léa Maria Macruz Ferreira Demarchi

Comment

The hypertrophic cardiomyopathy (HCM) is defined as a genetic primary cardiomyopathy, morphologically characterized by non-dilated hypertrophy of the left ventricle, in the absence of another systemic or heart disease capable of causing such ventricular alteration, such as systemic arterial hypertension and aortic valve stenosis[34].

It has a comprehensive clinical spectrum and broad morphological and symptomatic variability and risk of complications such as sudden death and heart failure[35].

The main anatomic characteristics of the HCM were obtained from the observation of necropsy data and are thus defined[34]: myocardial hypertrophy, spatial disarray of cardiomyocytes, intramural coronary arteries with obstructive alterations and myocardial fibrosis.

The myocardial hypertrophy can be asymmetric or symmetric. The most common form of presentation is the asymmetric one, characterized by more marked hypertrophy of the ventricular septum, with the ratio between the ventricular septum and the LV lateral free wall ≥ 1.3[36].

When located in the basal portion of the ventricular septum, the hypertrophy causes left ventricular outflow tract obstruction and, consequently, thickening of the mitral anterior cusp and subaortic septal endocardial fibrosis. Due to the constant friction between the valve leaflet and the septal endocardium, the endocardial fibrosis can acquire the format of the mirror image of the anterior cusp of the mitral valve.

The symmetric form is characterized by concentric hypertrophy of the left ventricle, without obstruction of the ventricular outflow tract.

In HCM, the spatial disarray of the cardiomyocytes must be present in more than 20% of the histologically sampled areas[37] and is characterized by multiple and chaotic intercellular connections, as right and oblique angles[34]. It can be found in any wall of both ventricles and more often occupies large portions of the LV. Extensive areas of disarray are described in young patients that died due to the disease[34].

The intramural coronary arteries present obstructive alterations characterized by thickening of the wall and lumen narrowing, due to the increase in collagen deposition in the intima and media layers. Such alterations, associated with the disproportion between the ventricular mass hypertrophy and the coronary circulation, result in myocardial ischemia and consequent fibrosis, which can be either focal or transmural[34].

Another frequent finding in HCM is the intramural trajectory or "myocardial bridge" of the anterior interventricular branch
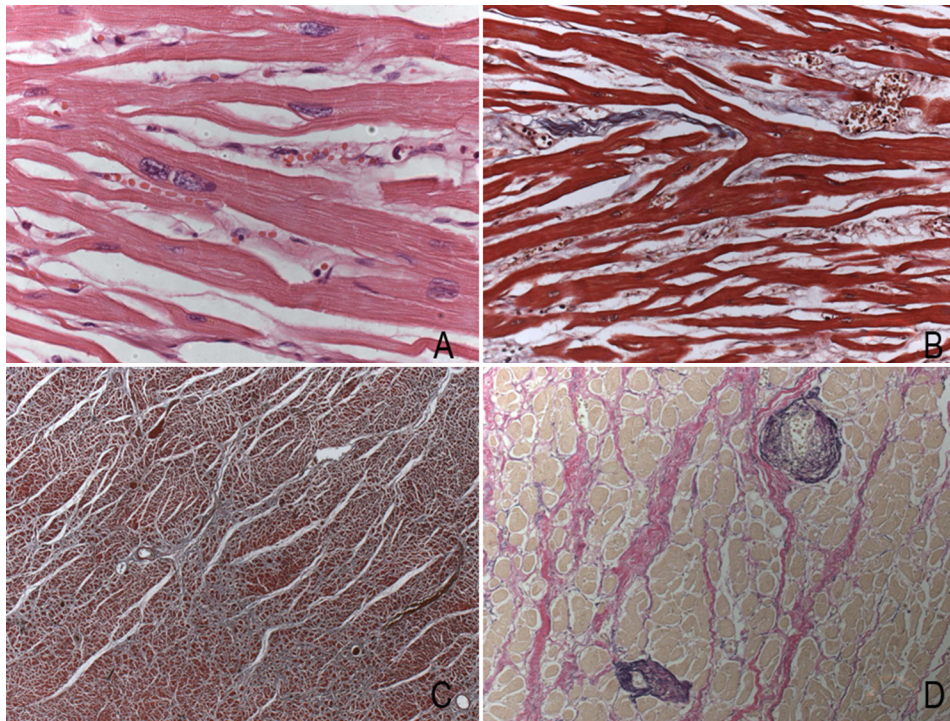
Figure 8 - Optical microscopy of histological sections of the LV myocardium: A) myocardial hypertrophy (hematoxylin-eosin, magnification: 40x). B) Spatial disarray of cardiomyocytes (Masson's trichrome, magnification: 20x). C) Diffuse myocardial fibrosis (areas stained blue by Masson's trichrome, magnification: 2.5x). D) Decrease in the lumen and intima-media thickening of the wall of intramyocardial branches of coronary arteries (Miller's staining for elastic fibers, magnification: 20x).

of the left coronary artery, which has also been observed in this patient, although its physiopathological meaning is yet to be fully clarified[38].

The contribution of the endomyocardial biopsy (EMB) for the diagnosis of hypertrophic cardiomyopathy is quite limited and, in the present case, it did not show myocardial disarray, but only cardiomyocyte hypertrophy. In HCM, the areas of disarray are frequently located in deeper regions of the ventricular wall, distant from the subendocardial region

and, therefore, out of reach of the bioptome. However, the EMB is quite useful for the differential diagnosis with other causes of ventricular hypertrophy, such as amyloidosis, Pompe disease and even neoplasias[37,39].

The anatomopathological findings of the necropsy, associated with the clinical data and complementary examinations were crucial for the diagnosis of HCM in this patient.

Dr. Léa Maria Macruz Ferreira Demarchi

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