A 20 Year-old Man with Heart Failure Due to Restrictive Cardiomyopathy

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A 20-year-old man (born 10/16/1985), from the town of Dona Ines (state of Paraiba, northeastern Brazil), was admitted at the hospital due to mild effort dyspnea (2006).

The patient had presented shortness of breath triggered by mild effort since the age of 13 (1998); at this time, he also presented an episode of syncope while running. Since then, there was a slow progression of the dyspnea. He felt tired and dizzy when walking around 100 meters on level surfaces and he started to present lower-limb edema.

He also complained of diffuse joint pain. A heart murmur was diagnosed. He had received the diagnosis of rheumatic fever at 16 years of age (2001).

At the age of 18 (September 2004) he presented a picture of coughing and yellow expectoration, which was treated as pneumonia; subsequently, he sought hospital treatment.

The physical examination (2004) showed: weight = 60 kg; height = 1.76 m, pulse = 102 bpm, blood pressure (BP) = 96 / 74 mmHg. Pulmonary semiology was normal. The assessment of the precordium showed shock palpated on the 5th intercostal space, on the left hemiclavicular line. The heart sounds were normal. There was a ++ systolic murmur in the mitral area. At the abdominal assessment, the liver was palpated at 9 cm from the right costal border. He presented lower-limb edema.

The medications were maintained - 25 mg of hydrochlorothiazide, 40 mg of furosemide, 50 mg of captopril, 25 mg of atenolol daily and a monthly administration of benzathine penicillin IM .

The Electrocardiogram (ECG) (Sept 23, 2004) disclosed sinus tachycardia (107 bpm), left atrial overload and QRS axis at 90° parallel to the frontal plane, little prominent and non-progressive R waves in V_5 and V_6, suggesting right ventricular overload (Figure 1). The echocardiograms (2004, 2005 and 2006) showed biatrial dilatation and mitral and tricuspid valve prolapse. The Doppler examination showed moderate mitral and tricuspid failure. The last echocardiographic assessment (2006) showed right ventricular dilatation and hypokinesis (Table 1).

The chest x-ray (June 2005) showed bilateral pleural thickening with sparse calcification. The pleural thickening was more marked on the left, where the heterogeneous and loculated content could be observed, with areas of atelectasis in the adjacent pulmonary parenchyma. An increased number of mediastinal and axillary lymph nodes were identified to the left. The heart presented normal morphology and dimensions. The aorta had a normal caliber and regular contours, with no signs of dissection. Hepatomegaly and bilateral gynecomastia were also diagnosed.

After two years, the fatigue persisted and the patient presented worsening of the lower-limb edema that reached the thigh root as well as scrotal edema. The patient sought emergency care and a diagnosis of atrial fibrillation was made. The dose of diuretics was increased and warfarin was associated to the therapy. Two weeks later, during an ambulatory visit, edema persistence and INR increase to 11.1 were observed. The patient was then admitted to the hospital.

The physical examination (March 7, 2006) showed a pulse of 80 bpm and a BP = 100/80 mmHg. Pulmonary semiology was normal. The examination of the heart showed a ++ systolic murmur in the mitral area. The liver was palpated at 5 cm from the right costal border. The patient presented lower-limb edema that involved thighs and scrotum.

The laboratory assessment results of the last hospital admission are shown in Table 2. Blood and urine cultures did not show any growth of microorganisms.

The venous ultrasonography of the lower limbs did not identify signs that were suggestive of venous thrombosis.

During evolution (March 31, 2006), the patient presented sudden-onset shock, which was unresponsive to the administration of volume. Vasoactive drugs were administered and orotracheal intubation was necessary. The patient was transferred to the Intensive Care Unit (ICU).

A presumptive diagnosis of septic shock was made and antibiotic therapy was started with cefepime and vancomycin (April 1, 2006), posteriorly modified to meropenem, vancomycin and azithromycin.

The pulmonary artery angiotomography (April 4, 2006) did not show filling defects in the pulmonary artery and its branches. The dimensions of the pulmonary trunk and its

Key Words

Heart failure; pericarditis, constrictive; cardiomyopathy, restrictive; sarcoidosis; amyloidosis.

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branches were normal. There were bilateral pleural effusions, more marked on the left side and pleural calcifications and subsegmental atelectasis of the lower and upper lobes in both lungs.

The transesophageal echocardiogram (April 4, 2006) did not images suggestive of intracavitary thrombi or valvular vegetation. A patent foramen ovale was diagnosed with left-right flow and intense auto-contrast in the right atrium and ventricle and left atrium. The mitral valve was thickened, with prolapse of the anterior cuspid. The Doppler examination showed eccentric mitral valve insufficiency of moderate degree. There was mild tricuspid insufficiency.

Renal failure and anuria ensued and hemodialysis was initiated (April 9, 2006). Chest ultrasonography (April 6, 2006) did not show pleural effusion. Abdominal tomography (April 10, 2006) showed a lobulated liver contour and hyperattenuation of the parenchyma, ectasia of the hepatic veins and inferior vena cava and moderate ascites. The patient presented a new hemodynamic worsening with shock and fever during the evolution (April 20, 2006). The echocardiogram (April 20, 2006) did not show any alterations when compared to the previous one. All catheters were replaced, meropenem was substituted by tazobactam and sulfametoxazol-trimetoprima was associated.

In spite of the treatment, the patient developed bradycardia and hypotension and presented cardiac arrest in asystole, which was initially reverted (April 21, 2006). However, the patient remained in persistent shock during the evolution and underwent another cardiac arrest in asystole, which was unresponsive to resuscitation maneuvers and died on April 23, 2006.

Clinical aspects

This is a case of progressive congestive heart failure in a young individual, whose symptoms started at 13 years of age, accompanied during the evolution by findings of the involvement of other organs and systems: arthralgia, chronic hepatopathy (bilateral gynecomastia, ascites and hyper-attenuation of parenchyma), evidence of chronic pleura-pulmonary inflammatory involvement (pleural effusion, with thickening and calcifications, preceded by a picture of productive coughing) and enlarged mediastinal and axillary lymph nodes.

The clinical findings of progressive ascending edema and hepatomegaly, as well as the complementary examinations (electrocardiogram and echocardiogram) suggested a predominant involvement of the right ventricle, overload and dilatation of both atria, with normal systolic function and left ventricular dimensions. These characteristics corroborate the diagnosis of cardiopathy with diastolic restriction, with constrictive pericarditis being an important differential diagnosis to be considered, especially because the treatment is radically different. This differentiation can be difficult, as these conditions share similar characteristics.

Several inflammatory processes can cause constrictive pericarditis, but the more frequent etiologies are infectious, post-surgical and radiation exposure. The etiology can also be idiopathic, autoimmune/inflammatory (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, sarcoidosis) and neoplasic[1]. Tuberculosis was the most common cause in developed countries before the appearance of effective drug treatments.

The pericardial fibrosis prevents the filling of all cardiac chambers. Systemic venous congestion and decrease in the cardiac index occur, due to the ventricular filling impairment. The systemic congestion can lead to cardiac cirrhosis. There is also an increase in the pulmonary venous pressures and dyspnea, orthopnea and coughing can occur. Atrial fibrillation and tricuspid regurgitation can also occur. The ECG usually shows unspecific T wave alterations and voltage decrease, in addition to signs of left atrial overload or atrial fibrillation. The chest x-ray shows right atrial enlargement. The echocardiogram, in a small number of patients, can disclose pericardial calcifications and pericardial effusion.

The constrictive pericarditis, differently from the restrictive cardiomyopathy, can present a paradoxical pulse in one-third of the cases, pericardial beat, equalization of the filling pressures on the left and right sides, septal convexity

Table 1 - Echocardiographic findings

	2004	2005	2006
Aorta (mm)	23	25	25
Left atrium (mm)	54	52	52
Right ventricle	Normal	Normal	Dilated Hypokinetic
Left ventricular diastolic diameter (mm)	42	45	42
Left ventricular systolic diameter (mm)	29	30	25
Left ventricular ejection fraction (%)	59	62	72
Interventricular septum (mm)	6	6	7
Left ventricular posterior wall (mm)	6	6	6
Mitral valve, Doppler	Moderate failure	Moderate failure	Moderate failure
Tricuspid valve , Doppler	Moderate failure	Moderate failure	Moderate failure
Estimated pulmonary artery pressure (mm Hg)	Elevated	45	45
Interatrial septum	-	-	Interatrial communication

Table 2. **Laboratory assessment**

	Mar 9 2006	Apr 4 2006	Apr 19 2006	Apr 22 2006
Hb (mg/dl)	15.4	14.6	10.2	9.8
Hematocrit (%)	48	45	30	28
VCM (μm³)	87	88	86	88
Leucocytes /mm³	12,400	32,100	32,700	39,400
Neutrophils (%)	90	93	94	81
Eosinophils (%)	1	0	0	0
Lymphocytes (%)	3	2	2	10
Monocytes (%)	6	5	4	9
Platelets/mm³	411,000	425,000	169,000	246,000
Creatinine (mg/dl)	0.9	1.2	2.5	4
Urea (mg/dl0	31	92	116	141
Sodium (mEq/l)	140	130	136	135
Potassium (mEq/l)	3.6	3.8	3.6	5.4
INR	2.8		1.29	
APTT (r)	1.58		0.91	
Total Bilirubin (mg/dl)	1.2		8.23	5.09
Direct Bilirubin (mg/dl)	0.5		6.86	5.52
ALT (U/l)			64	53
AST (U/l)			54	
Gamma - GT (U/l)			662	610
Amylase (U/l)			110	
Alkaline phosphatase (U/l)			470	440
Arterial Lactate (mg/dl)			22	
Total protein (g/dl)			4.2	
Albumin			2.1	
Alpha 1-globulin			0.3	
Alpha 2-globulin			0.6	
Beta-globulin			0.7	
Gamma-globulin			0.5	

in protodiastole and increased pericardial thickness at the echocardiography. In restrictive cardiomyopathy, in comparison to constrictive pericarditis, we can observe: increased ventricular wall thickness, pulmonary artery systolic pressure > 50 mmHg, palpable *ictus cordis*, higher filling pressures, usually > 25 mm Hg, and at least 3-5 mmHg higher on the left than on the right, as well as prominent biatrial increase[2,3]. The last three characteristics make the diagnosis of restrictive cardiomyopathy the most likely in this case. However, the results of the imaging assessment such as computed tomography and magnetic resonance would be more decisive in the differentiation, as they provide a better assessment of the occurrence of pericardial thickening or calcification.

The patient presented a patent foramen ovale (PFO) as echocardiographic finding. Most patients with a PFO are asymptomatic. The most important potential clinical manifestation is the ischemic cerebrovascular accident due to paradoxical embolism[4]. The PFO with a right-left shunt can also be associated to migraines. The left-right shunt does not occur in PFO, as long as the septum *primum* remains competent. Patients in whom the foramen becomes patent, for practical purposes, are considered as having an interatrial communication (IAC). In IAC, the degree of left-right shunt depends on the size of the defect and the relative filling properties of the two ventricles. Diseases that cause a decrease in ventricular compliance or increase the left atrial pressure tend to augment the shunt. In the present case, the left-right shunt through the PFO could be justified by higher filling pressures on the left, a characteristic of restrictive cardiomyopathy.

Most children with IAC are asymptomatic and the diagnosis is made after a murmur is detected. When the increase in the pulmonary flow is very intense, congestive heart failure occurs and repeated respiratory infections can arise. In adults, the most common symptoms are intolerance to exercise and palpitations (mainly by atrial fibrillation or flutter). In older patients, the presenting symptom can be right ventricular failure. Considering that the patient in question has only a PFO, the low left-right flow does not justify all the described hemodynamic alterations as well as the systemic alterations.

The involvement of other organs and systems, as previously exposed, favors the hypothesis that the restrictive process is caused by a systemic disease that infiltrates the myocardium through the deposition of anomalous or inflammatory content, with the idiopathic variant being the least likely. Considering the aforementioned facts, the main diagnostic hypotheses are: sarcoidosis, amyloidosis, hemochromatosis and Fabry's disease. Another possibility of restrictive cardiomyopathy is endomyocardial fibrosis.

The first diagnosis given to the patient, i.e., rheumatic fever, does not apply to this case, although it is the most common worldwide cause of acquired heart disease in children and young adults. In addition to the lack of clinical or laboratory evidence of preceding infection by Group A streptococcus, the arthralgia, a possible minor manifestation of rheumatic fever occurred three years after the onset of the heart failure symptoms. In rheumatic fever, the joint involvement occurs early in the natural history of the disease, taking place around three weeks after the streptococcal infection. The mitral insufficiency murmur, along with the echocardiographic findings, must be attributed to the mitral prolapse instead of rheumatic involvement, as the echocardiogram performed six years after symptom onset would have disclosed evidence of valvular fibrosis or calcification. Therefore, as there was not enough evidence to attribute these findings to rheumatic carditis, we ruled out this diagnostic possibility (absence of two major Jones criteria or a major and two minor ones)[5,6].

Amyloidosis is a disease that results from the deposition of amyloid fibrils formed by protein in tissue. In its primary form, these proteins are light-chain immunoglobulins (AL-type) produced by a population of plasmocytes, usually as a consequence of multiple myeloma. The secondary form (AA) occurs by the deposition of non-immunoglobulin proteins

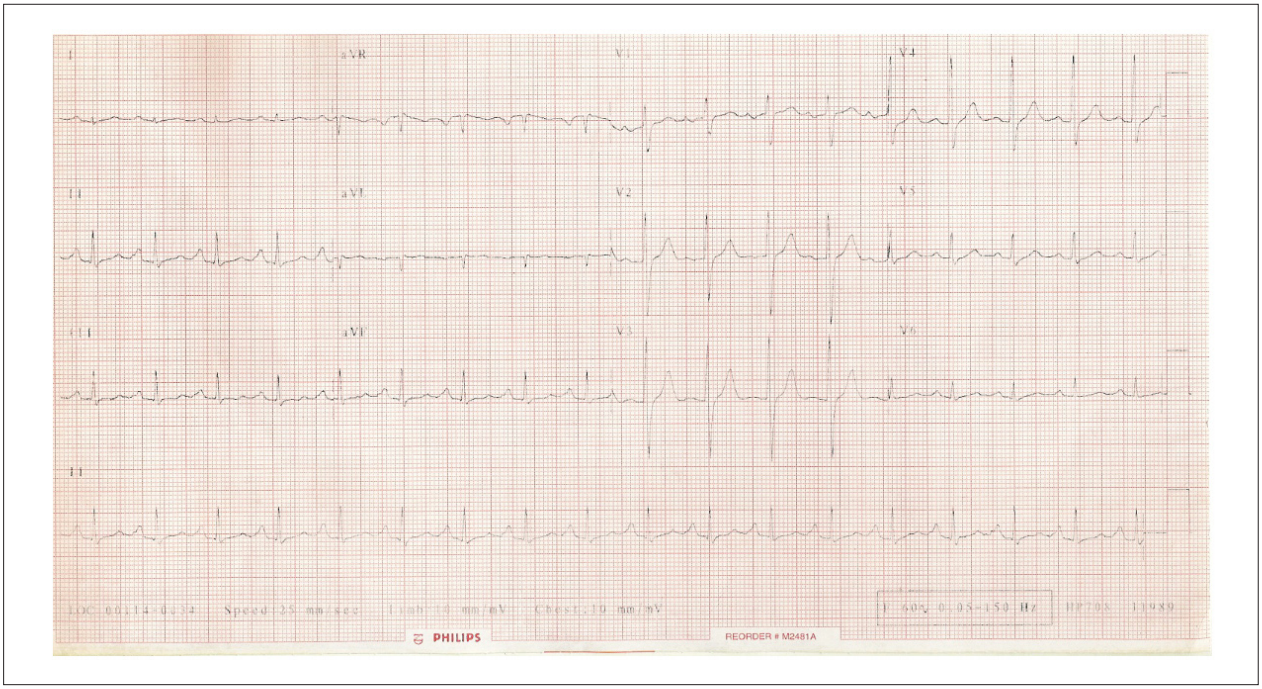

Figure 1 - ECG. Sinus tachycardia, left atrial overload and right ventricular overload.

and is found in individuals with chronic inflammatory or infectious diseases. It can affect any organ, but the main sites of amyloid deposition that are clinically important are the kidneys, the liver and the heart. Nephrotic syndrome, hepatomegaly, peripheral neuropathy, macroglossia and subcutaneous nodules are commonly found. The most common form of presentation of cardiac amyloidosis is the restrictive cardiomyopathy. However, the onset of cardiac disease symptoms is rare before the fourth decade of life[7,8]. In the present case, there is no evidence of kidney or neuropathic involvement and other systemic manifestations predominate. Additionally, the electrocardiographic and echocardiographic findings that are more characteristic of amyloidosis do not occur either: presence of low-voltage QRS complexes and thickening of the ventricular walls, respectively[8]. These data make this diagnosis less likely in the present case.

Hemochromatosis is characterized by the excess deposition of iron in the parenchymatous tissues (heart, liver, gonads and pancreas). It can occur as an autosomal recessive or idiopathic disorder, in association with hemoglobin synthesis defects due to inefficient erythropoiesis, chronic liver disease and excess oral ingestion or parenteral infusion of iron for many years[9]. The cardiac involvement leads to the combined pattern of dilated cardiomyopathy and restrictive cardiomyopathy, with systolic and diastolic dysfunction. The myocardial damage is attributed mainly to the direct toxicity of free iron and not simply to tissue infiltration. Heart dilatation occurs, with increased ventricular thickness. The findings are more prominent in the ventricular myocardium and the cardiac conduction system is commonly affected. This patient does not present increased ventricular thickness or ventricular dilatation, making this hypothesis unlikely.

Fabry's disease is a hereditary disorder with an X-linked recessive pattern of inheritance that results from abnormalities of alpha-galactosidase A deficiency, a lysosomal-enzyme, which is caused by more than 160 mutations[10]. Some mutations result in undetectable enzyme activity, with manifestations throughout the body, whereas others produce some degree of enzyme activity, resulting in variants of which involvement is limited to the myocardium, only. The disease is characterized by an intracellular accumulation of glycosphingolipids, with marked skin, kidney and myocardial involvement in the classic form. The vascular endothelium is affected, as well as conduction tissue and valves, particularly the mitral valve. The major clinical manifestations result from the accumulation of glycosphingolipids in the cellular endothelium, with the eventual occlusion of small arterioles. Angina pectoris and myocardial infarction occur, although the coronary arteries show a normal angiographic aspect most of the times. There is an increase in left ventricular thickness, producing usually mild diastolic dysfunction, with preserved systolic function and mitral insufficiency, without clinical significance. The symptomatic cardiovascular involvement occurs in almost all male patients, whereas female patients present mild or absent symptoms. Arterial hypertension, mitral prolapse and congestive heart failure are common findings. The differentiation from other hypertrophic and restrictive processes may not be possible through the echocardiography. The patient in the present case does not present cutaneous or renal manifestations, in addition to the lack of symptoms of myocardial ischemia and ventricular hypertrophy.

Endomyocardial fibrosis (EMF) is common in tropical countries and occurs more often in children and young adults. It is characterized by endocardial fibrosis of the

inflow tract of one or both ventricles. Biventricular disease occurs in almost half of the cases; 40% of the cases present isolated left ventricular involvement and 10%, isolated right ventricular involvement[9,12]. There is an inconstant association with eosinophilia. The left ventricular involvement results in pulmonary congestion symptoms, whereas the right ventricular involvement can present characteristics of a restrictive cardiomyopathy and also mimic a picture of constrictive pericarditis. The failure of one or both atrioventricular valves frequently occurs[13]. The electrocardiographic and echocardiographic findings include: decreased QRS complex voltage, pericardial effusion, apical obliteration and increased endocardial echo reflectivity[12]. These last findings were not found in the present clinical case and the endomyocardial fibrosis does not explain the joint and pleuropulmonary involvement, either.

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by the involvement of several tissues by non-caseous granulomas[9,14]. It typically affects young adults between 10 and 40 years of age and presents with the following findings: bilateral hilar adenopathy, reticular pulmonary opacities, joint, eye and skin involvement (especially erythema nodosum). Pleural effusion occurs in approximately 5% of the cases and has an exsudative pattern[15]. The primary cardiac involvement is uncommon, with clinical manifestations present in less than 5% of the patients. These include: conduction disorders, ventricular arrhythmias, syncope and sudden death. Heart failure is due to direct myocardial involvement by the granulomas and scar tissue and can manifest as dilated or restrictive cardiomyopathy, with a progressive course[16,17]. The physical examination may disclose systolic murmur, compatible with mitral or tricuspid insufficiency, due to valvular or papillary muscle infiltration, of which dysfunction can lead to prolapse[18,19]. The electrocardiogram is unspecific and can disclose T wave abnormalities, blockages or pathological Q waves. Other findings include pericarditis and *cor pulmonale*. The echocardiogram can show ventricular wall thinning and increased echogenicity[16,20]. The aforementioned clinical case presents clinical and morphological characteristics compatible with the diagnosis of cardiac sarcoidosis, not only due to the aspect of cardiac involvement, but also to the systemic involvement: young individual, presenting progressive heart failure, with joint, liver and pleuropulmonary involvement and the presence of mediastinal adenomegaly. The morphological

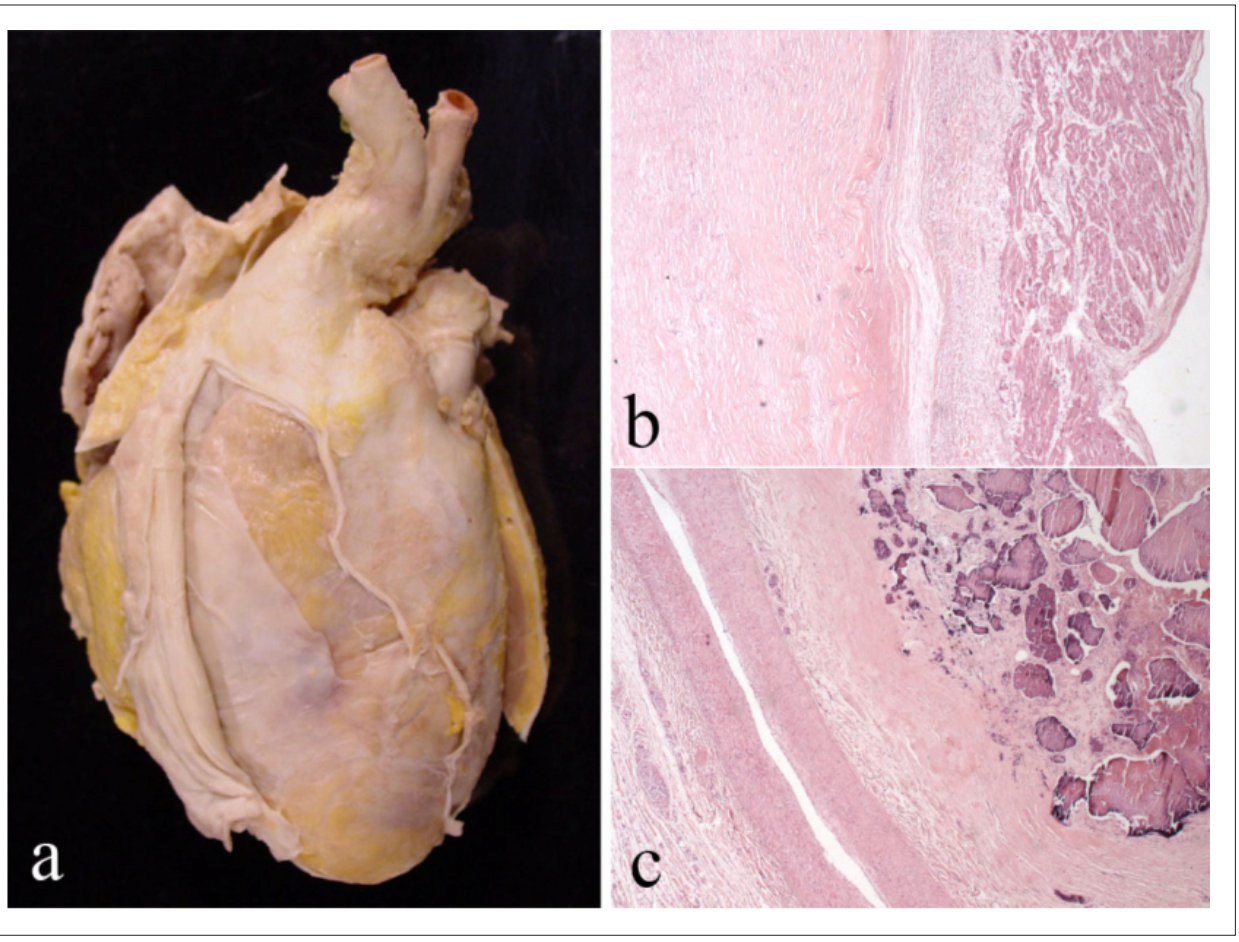

Figure 2 - A - External aspect of the heart, showing constrictive pericarditis with adhesions between the visceral and parietal leaflets; B - photomicrography of the heart on the atrial plane, where it can be observed that the pericardium (left side of the panel) is thicker than the myocardium (right side of the panel); C - photomicrography of the right atrioventricular annulus, showing a calcified nodule (right side) adjacent to the right coronary (left side). Panels B and C, hematoxylin and eosin stain; 2.5X magnification.

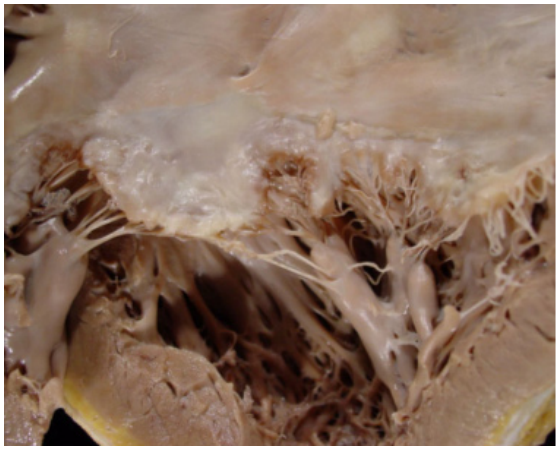

Figure 3 - Macroscopic aspect of the mitral valve, with slight thickening of the free border.

findings of biatrial enlargement with preserved left ventricular function, ventricular walls with preserved thickness, pulmonary hypertension (that could be explained in part by *cor pulmonale*) and valvular prolapse are also compatible. Therefore, we considered cardiac sarcoidosis as the main diagnostic hypothesis for the present case.

The clinical evolution was markedly altered after the onset of atrial fibrillation, significantly worsening the clinical picture and precipitating the hospitalization, which is common in restrictive cardiomyopathy due to the worsening of diastolic dysfunction. The death occurred after infectious complications of this hospitalization, due to septic shock and multiple system and organ dysfunction.

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Diagnostic Hypothesis: restrictive cardiomyopathy secondary to cardiac sarcoidosis.

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Necropsy

The main finding in this patient was fibrosing polyserositis, with the involvement of the pericardium, pleura (bilaterally) and peritoneum in the region of the liver, pancreas and gallbladder, as well as in the fundus of the urinary bladder. There was no retroperitoneal fibrosis.

The heart was involved by a dense and fibrous outer layer around the atria and ventricles, with firm adherences between the two pericardial leaflets (Figure 2). The pericardial thickness was higher than the myocardial thickness in some regions, especially in the atria and right ventricle. There was a calcified nodule in the in the lateral margin of the right atrioventricular annulus with a diameter of 0.4 cm. The atrioventricular and arterial valves did not present significant macroscopic alterations, except for the presence of small fibrous thickening in the annulus and the free border of the anterior leaflet of the mitral valve (Figure 3). The foramen ovale was patent for 0.6 cm. The pleuras presented diffuse thickening (Figure 4) and multiloculated areas, mainly in the pulmonary bases.

The diaphragm was firmly adhered to the liver and there was a narrowing of the inferior vena cava orifice in the diaphragmatic plane. The gallbladder was small and was encased by dense fibrosis of the hepatic hilum. The cut surface of the liver had a diffuse nodular aspect (Figure 5). The spleen was also surrounded by dense fibrosis, as well as the pancreas in its anterior face and the fundus of the urinary bladder.

Histologically, all serous membranes presented dense fibrosis with very slight inflammatory infiltrate by mononuclear cells (Figure 2). There were no signs of the process activity, except around the multiloculated areas of the pleura that presented fibrinous exudate.

Myocardial cross-sections showed cardiomyocyte atrophy. The mitral valve presented slight fibrosis, with no inflammatory signs. The calcified nodule in the right atrioventricular annulus was located very close to the right coronary, which seemed to be compressed by the nodular mass (Figure 2).

The histological assessment of the liver was compatible with

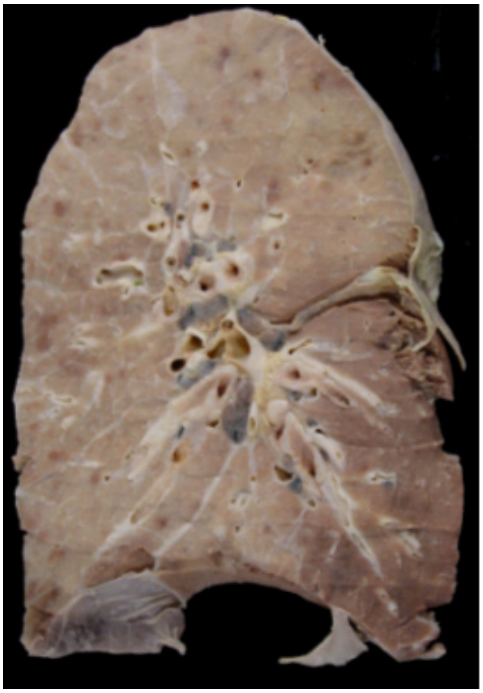

Figure 4 - Sectioned surface of the right lung, showing diffuse thickening of the parietal pleura and increased hilar lymph node volume.

"cardiac" cirrhosis (Figure 4), with the so-called "reversion of the hepatic lobes", a situation where the portal spaces are located in the center of fibrotic nodules and the center-lobular veins are surrounded by parenchymatous fibrosis.

Focally, there were rare fibrotic hyaline nodules (Figure 5). Moreover, histologically, the lungs showed chronic passive congestion and multiple hyaline nodules surrounded by inflammatory infiltrate to slight intensity mononuclear cells, interpreted as old granulomas (Figure 6). No parasitic residues, alcohol-acid-resistant bacilli or fungi were found in these lesions, as well as in the hyaline nodules of the liver.

The mediastinal lymph nodes presented marked congestion, with no signs of granulomatous inflammation in the analyzed sections

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Anatomopathological diagnoses: Chronic fibrosing polyserositis, with constrictive pericarditis and signs of high-intensity congestive heart failure.

Old granulomas, partially hyalinized in the lungs and liver; "Cardiac" cirrhosis

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Comments

From the anatomopathological point-of-view, the findings explain the patient's clinical presentation. However, it was

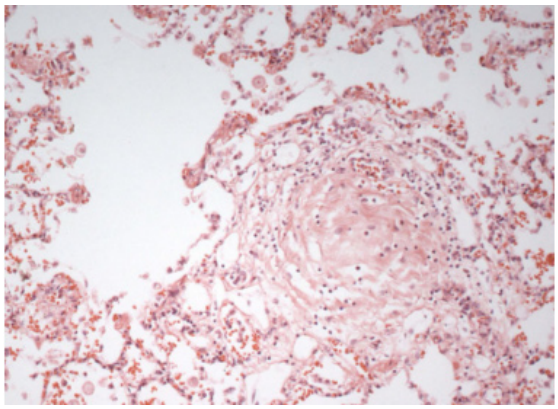

Figure 6 - Photomicrography of the lung showing a fibrous nodule surrounded by slight lymph-histiocytary infiltrate, interpreted as old granulomas. Hematoxylin-eosin stain, 10x magnification.

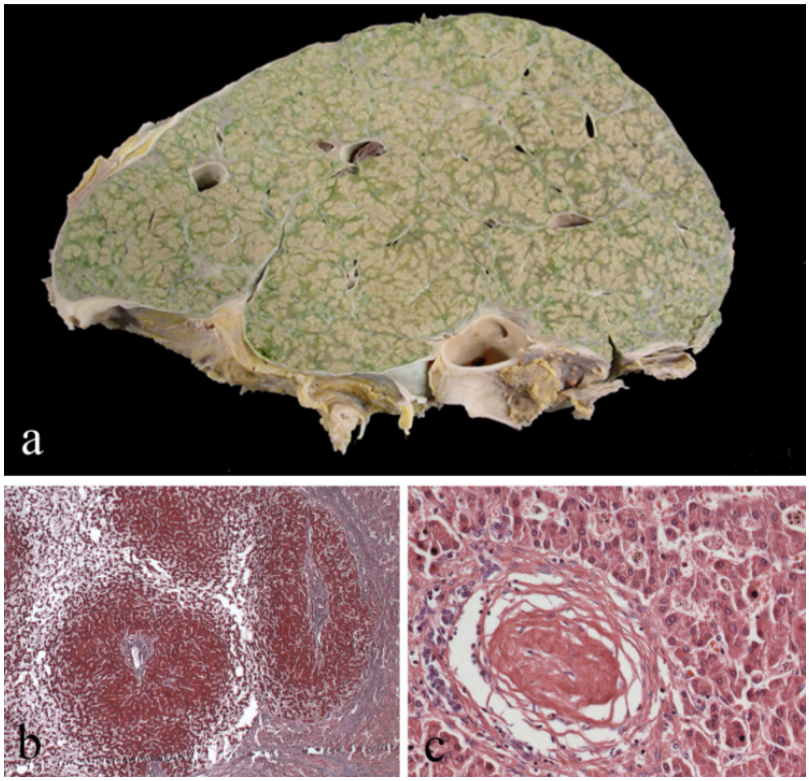

Figure 5 - Liver. A - Macroscopic aspect, with sectioned surface showing a nodular aspect and the fibrous thickening of the capsule; B - photomicrography showing the nodular aspect of the parenchyma; C - photomicrography showing a hyaline fibrous nodule. Panels B and C, Masson's trichrome stain; 2.5 and 20X magnification, respectively.

not possible to clarify the etiology of the generalized fibrosing process. The finding of partially hyalinized granulomatous nodules, although only in the lungs and liver, leads to the assumption that the same disease caused all the systemic fibrotic reaction.

In this context, the first hypothesis would be tuberculosis, which is a known cause of constrictive pericarditis. On the other hand, it does not usually course with dense fibrosis of other serous membranes. Another possibility would be mansonic schistosomiasis, an endemic disease in some regions of our country that also presents hepatic and pulmonary granulomas as a reaction to the parasite eggs. A third, more remote possibility for granulomatous disease would be sarcoidosis; however, the presentation would be totally atypical, due to the lack of ganglionar and myocardial involvement.

The literature reports some cases of systemic fibrosing reaction associated to fibrotic nodules/pulmonary granulomas.[21-23] The pathogenetic association between the two findings, however, remains to be clarified.

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