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Case 5 - A 73 Year-Old Man with Heart Failure, Preserved Systolic Function and Associated Renal Failure

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Male patient, 73 years old, retired metallurgist, born in Alagoas, residing in Sao Paulo, sought medical attention for dyspnea on minimal exertion.

At his first visit to Instituto do Coração - Incor (18/June/2004) he complained of dyspnea that had begun 28 years before, initially triggered by great exertion; however, in the last two years it had progressed to dyspnea at minimal exertion and for the last month, it occurred even at rest and with orthopnea. These symptoms showed slight improvement with furosemide and digoxin.

He also reported chest pain on exertion, accompanied by sweating and nausea for the last five years before that consultation. The patient underwent a coronary angiography, which showed a 40% lesion in the anterior descending and first diagonal arteries and 50% lesion in the right coronary artery. The left ventricle was normal, with hypertrophic appearance, and he had pulmonary artery hypertension (systolic pressure of 50 mmHg).

The patient denied current smoking, alcohol consumption, arterial hypertension, dyslipidemia and diabetes mellitus. He underwent gastrectomy for peptic ulcer at 43 years of age and reported anemia requiring blood transfusion a month before.

He had a history of alteration in bowel movement with alternating diarrhea and constipation since the age of 69 and had lost 12 kg in recent months.

Physical examination showed a patient weighing 54.3 kg, height 1.68 m, BMI 19.2 kg / m^2, heart rate of 96 bpm, blood pressure 92 x 50 mmHg, jugular stasis + +/ 4 + at 45°. Pulmonary auscultation showed crackles at the bases; cardiac auscultation showed muffled heart sounds and holosystolic murmur at the lower sternal border; the liver was palpable three centimeters from the right costal margin and there was no edema or signs of poor peripheral perfusion.

Keywords

Heart Failure; Renal Insufficiency; Pulmonary Embolism.

Laboratory tests showed: potassium = 5.3 mEq/ L, sodium = 135 mEq / L, creatinine = 2.1 mg/dL, hemoglobin = 11.6 g/dL, hematocrit = 37%, leukocytes = 13,400 / mm ^{3} and negative serology for Chagas disease.

The ECG (June 15, 2004) showed sinus rhythm, 58 bpm HR, PR 220 ms, SAQRS (-) 20°, dQRS 86 ms, QT 450 ms, first-degree atrioventricular block, ST depression in V$_5$ and V$_6$ (with flattened or inverted T wave, suggestive of digitalis action) (Figure 1). Chest x-ray showed + + / 4 + cardiomegaly.

The digoxin dose was decreased to 0.125 mg; the dose of 40 mg of furosemide was maintained and 12.5 mg of hydrochlorothiazide were added, together with 40 mg of isosorbide and 100 mg of acetylsalicylic acid daily.

Echocardiography (May/2004) showed increased right and left atria, the latter measuring 48 mm, increased septal thickness (16 mm), normal left ventricular ejection fraction (66%) and pulmonary hypertension (pulmonary artery systolic pressure = 65 mmHg).

New laboratory tests were requested, as well as echocardiography, 24-hour Holter assessment and myocardial perfusion scintigraphy. However, they were not performed because the patient sought emergency medical care due to the persistence of dyspnea, onset of nausea and vomiting and increased abdominal volume on July 7, 2004.

Physical examination (July 07, 2004) showed the patient was in good general health status, slightly pale, heart rate of 64 bpm, blood pressure 90 x 60 mmHg; crackles heard at the lung bases; auscultation sounds were arrhythmic, no murmurs; abdomen: the liver was palpable 5 cm below the costal margin, hardened, extending to the epigastrium; bowel sounds were audible and there was no rebound tenderness; there was no lower-limb edema.

Laboratory assessment (07/jul/2004) showed urea = 173 mg/dL, creatinine = 4.4 mg/dL, potassium =5.9 mEq/L, hemoglobin = 11.1 g / dL, hematocrit = 34%, platelets = 284.000/mm^3, leukocytes = 6.800/mm^3 , normal coagulation, troponin = 0.82 ng/mL and CK-MB = 12.5 ng/mL. ECG (July 07, 2004) showed atrial fibrillation with ventricular rate of 60 bpm, ST depression with flattened or inverted T wave, suggestive of digitalis action (Figure 2).

The diagnoses of heart failure, digitalis intoxication, chronic renal failure with acute worsening of renal function and wasting syndrome were attained.

Digoxin use was discontinued, with volume and dobutamine being administered.

There was improvement in blood pressure, which increased to 100 x 60 mmHg, without worsening of dyspnea, and creatine
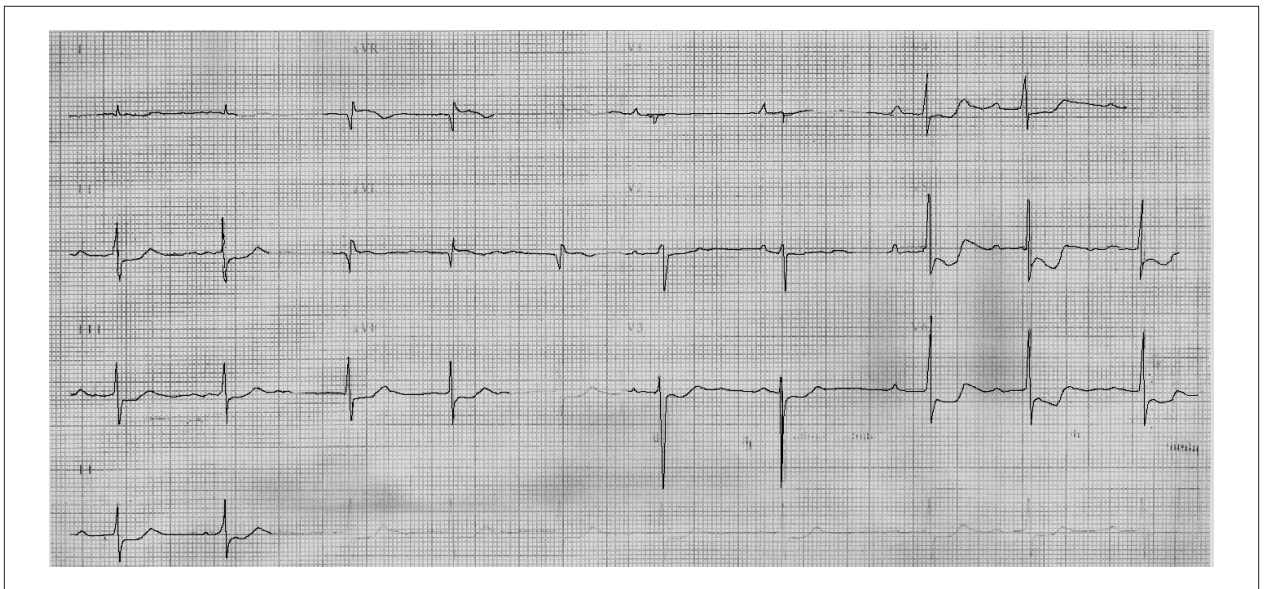
Figure 1 - *ECG – Sinus rhythm, first-degree atrioventricular block, ST depression in V5 and V6 (flattened or inverted T wave, suggestive of digitalis action).*
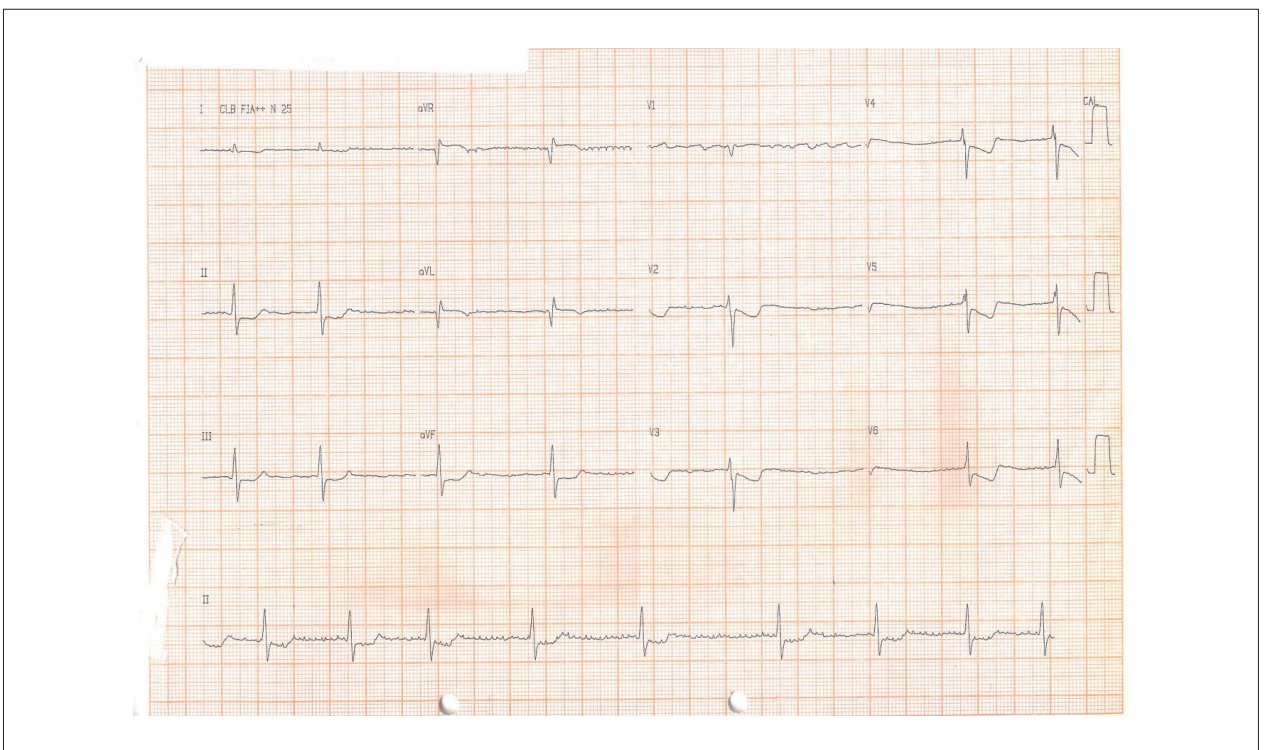

Figure 2 - *ECG – Atrial fibrillation, with bradycardia, ST depression with flattened or inverted T wave, suggestive of digitalis action.*

decrease. Dobutamine was discontinued on the 3rd day of hospitalization. The laboratory evolution is shown in Table 1.

Upper digestive endoscopy (July 20, 2011) showed esophageal tract of normal aspect, caliber and extension and the gastroesophageal junction 40 cm above the upper arch showed no signs of gastroesophageal reflux or hiatal hernia. In the distal third of the esophagus, there were three fine-caliber varicose veins, bluish, straight and without red spots. The stomach showed good expandability and was reminiscent of the Billroth-II gastrectomy, having usual proportions, with

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Table 1 - Laboratory assessment during hospitalization

	7/July	13/July	19/July	21/July
Hemoglobin (g/dL)	11,8	8,5	10,1	8,9
Hematocrit (%)	36	26	30	28
MCV (pg)	78	81	77	82
Reticulocytes/mm³	-	32.000	-	-
Leukocytes/mm³	7,100	9,700	5,800	4,500
Neutrophils (%)	88	92	60	95
Rods (%)	7	0	0	0
Lymphocytes (%)	7	3	2	1
Monocytes (%)	5	5	6	4
Platelets/mm³	320,000	188,000	131,000	105,000
Urea (mg/dL)	170	183	250	292
Creatinine (mg/dL)	4.5	3.7	4.5	5.5
Glucose (mg/dL)		74		67
Sodium (mEq/L)	135	135	137	139
Potassium (mEq/L)	5.3	5.5	5.2	5.7
Calcium (mEq/L0)		4.38		
Phosphorus (mg/dL)		5.8		
Magnesium (mEq/L0)		2.55		
Chloride (mEq/L)		112		
TSH (µUI/mL)		11.4		
Free T4 (ng/dL0)		0.7		
AST (U/L)		27		
ALT (U/L)		28		
AF (U/L)		329		
Gamma GT (U/L)		232		
Amylase (U/L)		65		
DHL (U/L0)		220		
CRP (mg/L)		28.4		
Total bilirubins (mg/dL)	0,72	0.63		
Direct bilirubin (mg/dL)	0,26	0.27		
Total proteins (g/dL0)		6.8		
Albumin (g/dL)		2.8		
Cholesterol (mg/dL0)		101		
HDL-C (mg/dL0)		42		
LDL-C (mg/dL0)		42		
Triglycerides (mg/dL0)		87		
INR		1.1		
APTT (rel)		0.95		
Venous gasometry				
pH			7.30	7.29
pCO_2 (mm Hg)			29	44
pO_2 (mm Hg)			37	32
Sat O_2 (%)			63.2	47.6
HCO_3 (mEq/L)			14	20.5
Base excess (mEq/L)			-11	-5.4

preserved pleated mucosa with no significant inflammatory reaction. There were no changes in the anastomotic mouth and segments close to the afferent and efferent loops. In conclusion, there were incipient esophageal varices; normal Billroth II partial gastrectomy and no hemorrhagic lesions.

The abdominal ultrasonography (July 11, 2004) had disclosed an enlarged liver, with blunt edges and heterogeneous texture with multiple nodular images with irregular borders; ectasia of hepatic veins and inferior vena cava, with no signs of intrahepatic or extrahepatic bile duct dilation and presence of voluminous ascites. The spleen was of normal size. Kidney size was at the lower limit of normal dimensions (right kidney and left kidney measured 8 cm and 9 cm, respectively), with more echogenic texture than the usual and alteration in the corticomedullary ratio - 0.9 cm to the right and 0.9 cm to the left. There were no calculi or hydronephrosis, but there were 1.7-cm simple cortical cysts in the upper pole of the right kidney and smaller ones, of up to 0.8 cm, in the left kidney.

Retroperitoneal visualization was not possible due to excessive intestinal gas.

He received packed RBCs on July 13, 2004. On the 19th, he had abdominal distension. On the afternoon of the 21st, he underwent CRA, resuscitated through reanimation and defibrillation techniques; he was submitted to intubation and was transferred from the Hospital Auxiliar de Cotoxó to Incor ER. The patient developed bradycardia and shock, and after new CRA in asystole, he died at 1 AM on July 22, 2004.

Clinical Aspects

This is the case of a 73-year-old patient with hypothyroidism, coronary artery disease, left ventricular hypertrophy, heart failure with preserved left ventricular ejection fraction and exacerbation of chronic renal failure. The patient's clinical picture had worsened in the last two years that preceded his last hospitalization, with progressive symptom worsening.

Among the possible causes for such clinical worsening, are: ischemic equivalent, pulmonary thromboembolism and the evolution of the underlying disease, which in this case corresponds to diastolic heart failure with preserved left ventricular ejection fraction. As for the ischemic equivalent, the patient's episodes of chest pain were not accompanied by typical manifestation of myocardial ischemic disease and additionally, they did not trigger changes in the hemodynamic balance[1]. Furthermore, the patient had no predisposing risk factors for coronary artery disease[2] and the coronary angiography showed no significant coronary lesions. Thus, the hypothesis of an ischemic event is weakened.

Regarding pulmonary thromboembolism, only the patient's age is a risk factor for pulmonary embolism, as observed in epidemiological studies[3]. Moreover, there was no clinical history consistent with hypercoagulability syndrome with recurrent thrombotic events, although such an association can only be ruled out after specific laboratory investigation for the most prevalent types of thrombophilia in the general population, which are factor V Leiden, hyperhomocysteinemia and antiphospholipid antibody syndrome, in addition to the less prevalent ones such as antithrombin III, protein C and S deficiency[4].

Clinical investigation of pulmonary thromboembolism involves echocardiography, perfusion and ventilation pulmonary scintigraphy, Doppler of lower limbs, pulmonary angiography, and in some cases, pulmonary arteriography, although in the present case only the echocardiography was performed. Therefore, there are no data to support this diagnosis.

For the differential diagnosis, systemic diseases that have renal and cardiac involvement (clinical situations that the patient had) were considered, e.g., systemic lupus erythematosus and schistosomiasis, in addition to hepatic neoplasms which, in this case, should be considered because of the patient's age, history of weight loss in recent years and the presence of liver nodules identified by computed tomography. However, there are no data to confirm this diagnosis.

Systemic lupus erythematosus can affect both renal and cardiac function and these may present with heart failure, such as myocarditis and Libman-Sacks endocarditis, but they do not cause diastolic heart failure, as in this case[5]. The high pulmonary artery systolic pressure (65 mmHg) makes the possibility of constrictive pericarditis caused by lupus even more remote.

Schistosomiasis is another cause of cardiac and renal involvement, with manifestations predominantly in the right heart chambers, pulmonary hypertension and even cor pulmonale[6]. The clinical picture of the patient, with gastrointestinal disorders, portal hypertension, hepatomegaly, ascites, and marked weight loss contributes to this diagnosis. However, the chronic form of cor pulmonale consists in a combination of right ventricle hypertrophy and dilation secondary to pulmonary hypertension, neither of which was identified in the patient.

As the last and main cause of clinical deterioration of the patient, is the evolution of the underlying disease itself, in this case, diastolic heart failure with preserved left ventricular fraction. Diastolic cardiomyopathy is characterized by changes in ventricular relaxation, with impaired ventricular filling and/or increased filling pressures and increased dependence on the atrial contraction phase[7]. There is an increase in left atrial pressure and, consequently, in the pulmonary veins and capillaries, as well as a decrease in stroke volume, signs present in this type of heart disease that explain exercise intolerance and even dyspnea at rest, referred by the patient. The evidence of diastolic dysfunction can be obtained from the hemodynamic data, levels of natriuretic peptides, echocardiographic and tissue Doppler data[8]. Among the main causes of left ventricular diastolic dysfunction are systemic hypertension with left ventricular hypertrophy, aortic stenosis with preserved left ventricular ejection fraction, hypertrophic and restrictive cardiomyopathies and coronary artery disease.

Hypertensive heart disease can be defined as the result of overload imposed to the LV by the increase in arterial pressure and peripheral vascular resistance, which causes structural changes in the LV that manifest as hypertrophy and total stiffness[9]; however, in this case, the patient did not have systemic arterial hypertension. As for aortic stenosis, there are no data to support the diagnosis.

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For the diagnosis of left ventricular hypertrophy, the electrocardiogram (ECG) is not a sensitive method, but quite specific. Still, the findings of the patient in this case do not meet these criteria. Echocardiography is a low-cost procedure and is considered the method of choice for non-invasive diagnosis of increased cardiac mass[10]. However, in this case, the patient had no criteria for hypertrophic cardiomyopathy at the echocardiography.

One must also emphasize the differential diagnosis between left ventricular hypertrophy and restrictive cardiomyopathy, especially with the low-voltage electrocardiogram in the frontal plane, present in the latter cardiomyopathy, which favors the storage disease and consequent restriction to ventricular filling[11].

The clinical findings of lower-limb edema and hepatomegaly, as well as the supplementary tests (electrocardiogram and echocardiogram), pointed to predominant RV involvement with overload and dilation of both atria and normal LV systolic function and dimensions. These characteristics corroborate the diagnosis of heart disease with diastolic restriction. Among the diseases that can cause restrictive cardiomyopathy[12] are storage diseases (hemochromatosis and Fabry disease), endomyocardial disease (endomyocardial fibrosis) and infiltrative diseases (amyloidosis and sarcoidosis).

Hemochromatosis is characterized by excessive iron deposits on parenchymal tissues (heart, liver, gonads, and pancreas). It can occur as an autosomal recessive or idiopathic disorder, in association with defects in hemoglobin synthesis due to ineffective erythropoiesis, chronic liver disease and excessive oral ingestion or parenteral administration of iron for many years[13].

Cardiac involvement leads to the combined pattern of dilated cardiomyopathy and restrictive cardiomyopathy with systolic and diastolic dysfunction. Myocardial damage is mainly attributed to direct toxicity of free iron and not only the tissue infiltration. Cardiac dilatation occurs with increased ventricular thickness. The findings are more prominent in ventricular than in atrial myocardium and it often affects the cardiac conduction system. In this patient, although he showed increased ventricular thickness demonstrated by the echocardiography, there was no ventricular dilatation or systemic manifestations of the disease, making this hypothesis unlikely.

Fabry disease is a genetic disorder with X-linked recessive inheritance, resulting from abnormalities linked to the deficiency of the lysosomal enzyme alpha-galactosidase A, which is caused by more than 160 mutations[14]. Some of them result in undetectable enzyme activity, which manifest throughout the body, while others produce some degree of enzymatic activity resulting in variants with limited involvement only in the myocardium. The disease is characterized by an intracellular accumulation of glycosphingolipids with marked involvement of the skin, kidneys and myocardium in the classic form. Involvement of the vascular endothelium occurs, as well as of conduction tissue and heart valves, particularly the mitral valve.

The major clinical manifestations result from the accumulation of glycosphingolipids in cell endothelium, with eventual occlusion of small arterioles. Angina pectoris and myocardial infarction occur, although in most cases, the coronary arteries have normal angiographic aspect. There is thickening of the left ventricle, producing usually mild diastolic dysfunction, with preserved systolic function and mitral regurgitation without clinical significance. The symptomatic cardiovascular involvement occurs in nearly all male patients, whereas the symptoms are mild or absent in females. The following are common findings: arterial hypertension, mitral valve prolapse and congestive heart failure. The patient of the present case had no skin manifestations, systemic arterial hypertension, or acute myocardial ischemia.

Endomyocardial fibrosis, common in tropical countries, most often occurs 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 the cases; 40% of them have isolated involvement in the left ventricle and 10%, isolated impairment of the right ventricle[13,15]. There is an irregular association with eosinophilia. LV impairment results in pulmonary congestion symptoms, while RV involvement may show characteristics of restrictive cardiomyopathy and also simulate constrictive pericarditis. Failure of one or both atrioventricular valves often occurs[16].

Electrocardiographic and echocardiographic findings include: decreased QRS complex voltage, pericardial effusion, apical obliteration and increased endocardial echo reflectivity[15]. The latter findings were not confirmed in this clinical case and, moreover, the endomyocardial fibrosis does not explain thyroid and renal involvement shown by the patient.

Being one of the causes of restrictive cardiomyopathy, sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by the involvement of various tissues by noncaseating granulomas[17].

Cardiac involvement is infrequent and primary clinical manifestations occur in less than 5% of patients, being characterized by conduction defects, ventricular arrhythmias, syncope and sudden death. The direct myocardial involvement by granulomas and scar tissue can manifest as dilated or restrictive cardiomyopathy, with progressive course[18]. The ECG is nonspecific and can show T wave abnormalities, blocks or pathological Q waves. Other findings include pericarditis and cor pulmonale. Echocardiography can disclose thinning of the ventricular wall and increased echogenicity[18]. Cardiac magnetic resonance is a highly sensitive and specific method for diagnosis. In our case, there were no suggestive alterations, making it unlikely that this was the patient's diagnosis.

And finally, systemic amyloidosis, which is a group of diseases that have extracellular deposits of insoluble fibrillar proteins consisting of low molecular weight subunits[5]. Clinically, it is classified as[5]: primary (AL), secondary (AA), hereditary and associated with old age (senile). AL amyloidosis is caused by the deposition of proteins derived from light chain fragments, in general, a monoclonal immunoglobulin (80.0% of cases). It may occur alone or in association with multiple myeloma (10.0% of cases). AA amyloidosis can complicate chronic diseases that course with recurrent inflammation. The fibrils consist of fragments of amyloid protein A, an acute phase protein.

There is also a hereditary-type amyloidosis (deposition of fibrils derived from transthyretin) and a senile form (also deposition of transthyretin). In this context, there can be amyloid infiltration in the thyroid, leading to hypothyroidism[19]; however, it most commonly occurs concomitantly with goiter, not described in the case. Another clinical manifestation, such as autonomic neuropathy due to amyloidosis[5], which courses with orthostatic hypotension, early satiety, change in bowel habits (diarrhea or chronic constipation) were observed in this patient.

AA amyloidosis affects the cardiovascular system in only 5% of cases and there is no mention of systemic inflammation (although serology for hepatitis are not available)[20]. Therefore, the two subtypes of amyloidosis most likely in this case would be AL and senile amyloidosis. There are important differences in the prognosis and rate of evolution between these subtypes: the median survival after cardiac involvement is, respectively, 11 and 75 months[21].

Furthermore, the insidious course of the disease is the rule for senile amyloidosis, whereas in AL, there is a rapid progression of symptoms and much higher cardiovascular involvement. In the absence of confirmation of plasma cell dyscrasia, the distinction between them is made through immunohistochemical analysis[22].

Cardiac involvement in cases of amyloidosis occurs in one third of patients. Right ventricular failure usually occurs, with little pulmonary edema, despite elevated filling pressures. There are, however, other alterations including atrial fibrillation, conduction disorders and electrically inactive areas. Still, high-grade atrioventricular blocks are uncommon[11]. Echocardiography is an important noninvasive test for the diagnosis of amyloidosis. LV wall thickening with evidence of diastolic dysfunction is the earliest alteration, which can progress to restrictive cardiomyopathy[23]. Biatrial enlargement and valve thickening may occur[19].

The diagnostic investigation includes collecting a urine sample to test for the presence of paraproteins. The detection of increased excretion of light chains with maintenance of the kappa/lambda ratio, in the absence of the monoclonal chain establishes the diagnosis of amyloidosis[20]. Although not confirmed by tests, the diagnosis of amyloidosis can be achieved through a biopsy[24], which can be performed in subcutaneous adipose tissue (sensitivity of 65 to 80%)[25] or in the endomyocardium (up to 97%)[26] with demonstration of amyloid deposits in tissues classically stained with Congo red. Therefore, due to the clinical picture of the patient and the complementary tests described, systemic amyloidosis is the most likely diagnosis of this anatomo-clinical discussion.

There was not enough time to evaluate the hepatic findings in the abdominal ultrasound, which may have contributed to the case outcome. (Dr. Tiago Rodrigues Politi)

Diagnostic hypothesis

Systemic amyloidosis with cardiac and renal involvement.

Other diagnoses: hypothyroidism and chronic renal failure. (**Dr. Tiago Rodrigues Politi**)

Necropsy

The patient had cachexia. The final factor triggering his death was pulmonary embolism in the lower lobe of the left lung. There was infarction in this territory (Figure 3) and acute infection in this and other areas of the lungs. Pulmonary thromboembolism was probably secondary to a clotting disorder, as, in addition to it, there was portal vein thrombosis and presence of thrombi that seemed to be recent (i.e., onset in the agonal period) in coronary arterial branches.

The main disease of this patient was hepatocellular carcinoma (Figure 4), underlying chronic hepatitis (Figure 5). The neoplasm is the likely cause of the bleeding disorder.

In addition to this disease, the patient also had cardiomyopathy, of which predominant clinical picture was atrial fibrillation (which can also be related to pulmonary thromboembolism, but there were no thrombi in the cardiac cavities). The fact that the ventricles did not show marked dilation, contrary to what happens with the atria (Figure 6), suggests that it is a case of restrictive cardiomyopathy. Among its possible causes are: amyloidosis, hypertrophic cardiomyopathy and ischemic heart disease. However, the absence of amorphous extracellular deposits, myocardial fiber disarray and severe obstruction of the coronary arteries go against such possibilities. Thus, the idiopathic form, with interstitial fibrosis, should be considered.

The patient also had atherosclerosis, with mild aortic and mild to moderate involvement of the coronary tree, but with no significant consequences. The kidneys had some degree of vascular alterations, which may be associated with atherosclerosis; kidney failure may have been associated with hepatorenal syndrome.

(**Dr. Paulo Sampaio Gutierrez**)

Anatomopathological diagnosis:

Main disease: hepatocellular carcinoma related to chronic hepatitis, probably viral.

Relevant secondary disease: restrictive cardiomyopathy.

Cause of death: pulmonary thromboembolism (**Dr. Paulo Sampaio Gutierrez**)

Comment

It is difficult in this case, to be sure that the pulmonary embolism, which was the final factor triggering death, was more related to heart failure or, as it seems likely, considering that such picture was well balanced and that there were no intracavitary thrombi, to hepatocellular carcinoma.

It is noteworthy the lack of a cancer diagnosis during the patient's life, corroborating data indicating that autopsies still currently disclose important diagnoses in a significant number of patients with heart disease[27].

Regarding the heart disease, amyloidosis is a possibility that should be considered in heart failure with restrictive pattern in the elderly. However, the clinical profile of patients with restrictive idiopathic cardiomyopathy[28] showed age variation of 10-90 years, with a mean of 64. Therefore, the patient fits into this description, not only regarding age but also concerning the atrial fibrillation, detected in 74% of patients. (**Dr. Paulo Sampaio Gutierrez**)
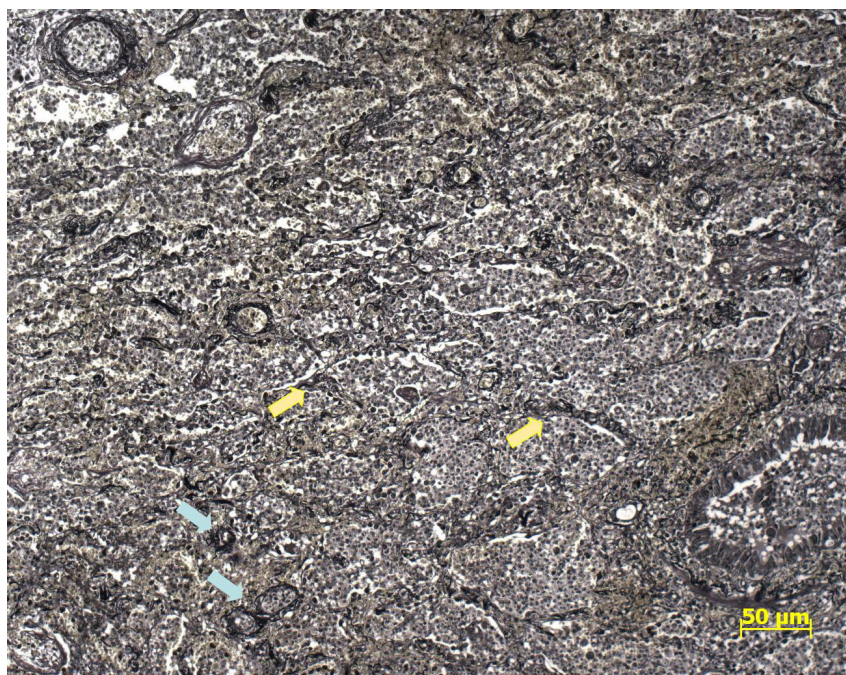
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Figure 3 - *Histological section of the lower lobe of the left lung with infarction, characterized by destruction of alveolar septa, of which there are only remnants of elastic tissue (yellow arrows). This tissue appears more intact around the small vessels (blue arrows). Verhoeff staining, magnification: 10x.*
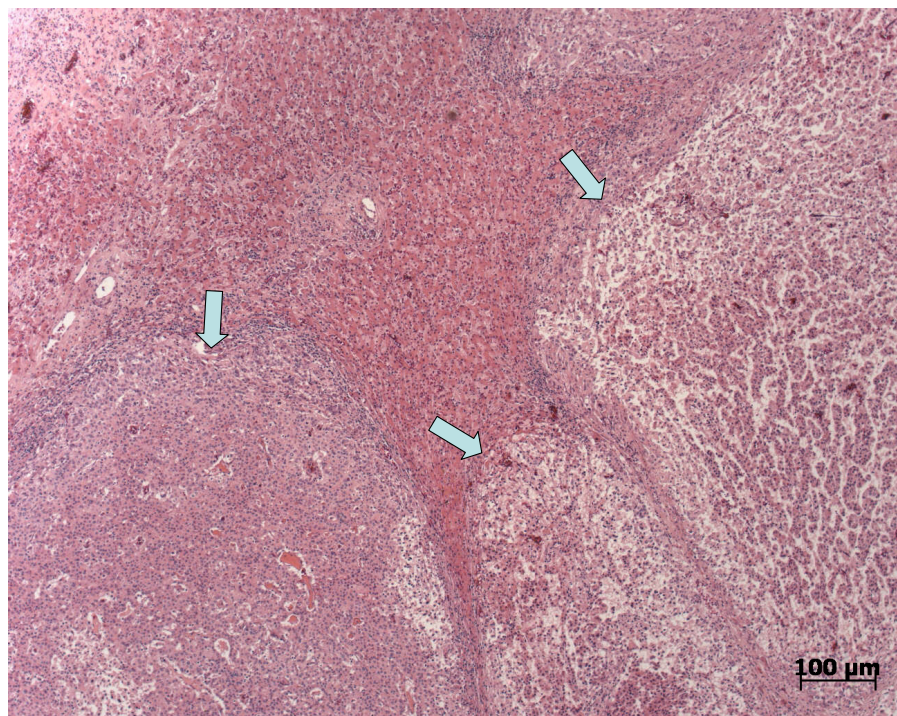

Figure 4 - *Histological section of the liver showing with hepatocarcinoma nodules consisting of cell cords (arrows), with the non-neoplastic tissue in the center, of more intense color and approximately stellar shape. Hematoxylin and eosin staining; magnification: 5x.*
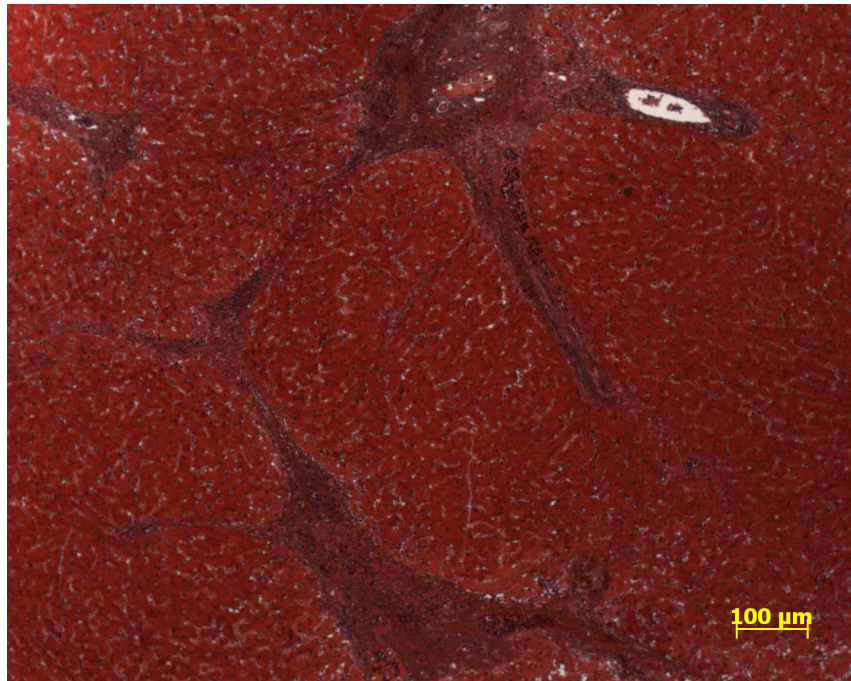
Figure 5 - *Histological section of the liver showing the formation of cirrhotic nodules, with darker borders. Masson staining; magnification: 5x.*
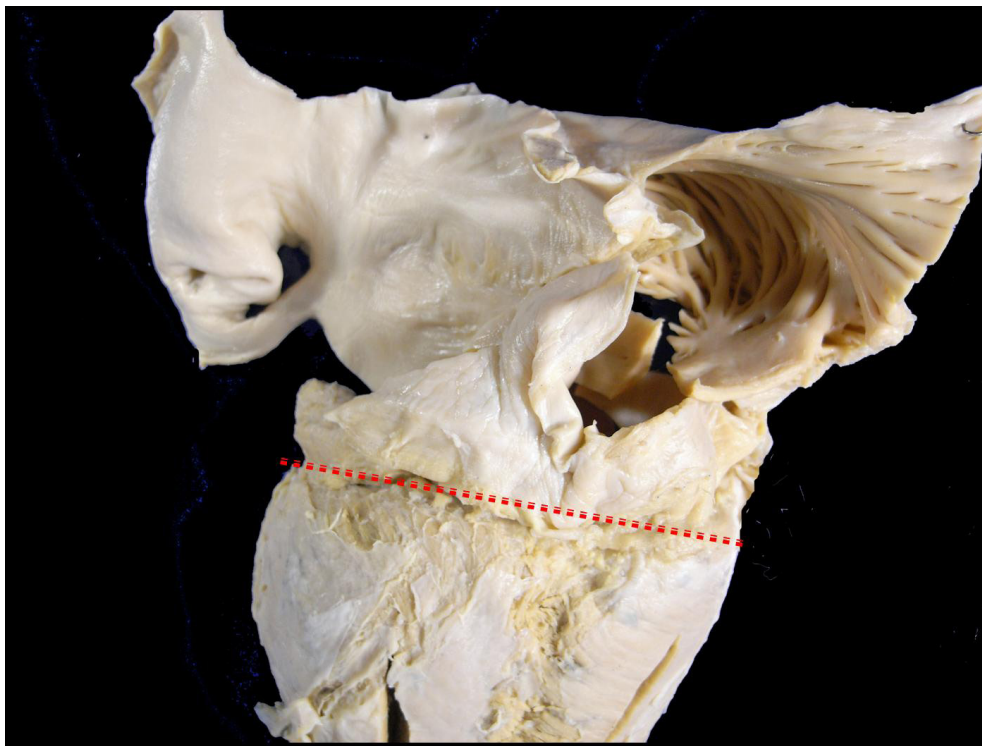

Figure 6 - *Posterior face of the heart. The double line roughly highlights the atrioventricular groove. Note the large atrial dilation, of which height equals or even surpasses that of the ventricles.*

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