

Case 5 50-Year-Old Woman with Restrictive Cardiomyopathy, Renal Failure and Proteinuria

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Woman with 50 years of age, born in Pernambuco, coming from São Paulo, sought medical assistance due to dyspnea caused by minor stress.

Four months ago, the patient presented signs of dyspnea caused by moderate effort, which 2 month ago progressed to minimum effort and orthopnea. The patient also presented edema on lower limbs. She sought medical assistance, was diagnosed with heart failure and was admitted for treatment. The patient knew she had hypothyroidism for years.

During admission, the patient underwent thoracentesis to drain pleural effusion. The biochemical analysis of the pleural liquid (6 Dec 2007) revealed lactate dehydrogenase (LDH) (pleural effusion/serum) $104/216 = 0.48$; protein (pleural effusion/serum) $2.8/6.2 = 0.45$; albumin gradient = 1.5.

The patient was discharged with prescription of 80 mg of Furosemide, 50 mg of Spironolactone, 75 mg of Captopril, 100 µg of levotiroxin on a daily basis, and 0.25 mg of Digoxin every other day.

Her dyspnea showed some improvement, however, some days later the dyspnea worsened again upon effort levels below the usual ones. The patient sought medical assistance in this Hospital.

Physical examination (9 Jan 2008) revealed eupneic patient, with increased jugular venous pressure, heart rate at 100 bpm and blood pressure 90 / 80 mm Hg. Lung examination revealed a decreased vesicular murmur on the right hemithorax middle third and abolition on the lower third of both hemithoraxes. Cardiac semiology revealed 4th heart sound, with no murmurs or pericardial friction rub. Her abdomen was painful to percussion in right hypochondrium region. Her liver was palpated at 10 cm from the right costal edge; there was edema +++/4+ on lower limbs.

Key words

Amyloidosis; Cardiomyopathy, Restrictive; Shock, Cardiogenic; Pulmonary Embolism.

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Chest radiography (9 Jan 2008) revealed a huge bilateral pleural effusion.

ECG (14 Jan 2008) showed sinus rhythm, cardiac frequency 100 bpm, left atrial overload, indirect right atrial overload signs (Peñaloza-Tranchesi), low voltage of frontal QRS, little progressive R wave of V_1 to V_4 (Figure 1).

Laboratory tests (9 Jan 2008) revealed increased creatinine levels (Table 1).

Echocardiogram (10 Jan 2008) revealed: aorta 29 mm, left atrium 41 mm, right ventricle diastolic diameter 29 mm, left ventricle dimensions (diastole/systole) 38 mm/28 mm, interventricular septum and posterior wall thickness of 13 mm and left ventricle ejection fraction of 52%. Moderate concentric hypertrophy was diagnosed. The patient presented hyper-refringency in the interventricular septum. Systolic ventricular function was depressed due to diffused hypokinesia. Doppler findings were compatible to restrictive pattern with no reversion after Valsalva maneuver. Right ventricle showed discrete hypertrophy and moderate hypokinesia and severe tricuspid valve insufficiency.

Pleural effusion puncture and drainage were made, as well as heart failure therapy with endovenous furosemide and maintenance of drugs under use.

The pleural analysis (16 Jan 08) revealed LDH ratios (pleural effusion/serum) $120/210 = 0.57$; proteins (pleural effusion/serum) $3.6/6.7 = 0.54$; albumin gradient = 1.2, 440 leukocytes/mm³, cholesterol <50 mg/dl, glucose 119 mg/dl

Abdomen ultrasound (14 Jan 08) revealed hyperechogenic area on hepatic lobe, the ultrasound aspect of which was compatible to haemangioma; besides small volume ascites and bilateral pleural effusion. No other alterations were found.

Ultrasound of urinary tract (22 Jan 2008) was normal.

Thorax tomography (17 Jan 2008) revealed a considerable bilateral pleural effusion with atelectasis of lower lobes and posterior segments of upper lobes.

Despite improvement of dyspnea, right pleural effusion persisted and a progressive worsening of renal functions was observed (Tab. 1). The patient kept a blood pressure at 90 / 60 mm Hg. Therapy with diuretic drugs, Captopril and Digoxin was stopped and Dobutamine was prescribed, along with hemodialysis and the patient was transferred to ICU.

Skin biopsy (16 Jan 08) was negative for amyloid substance (Congo red).

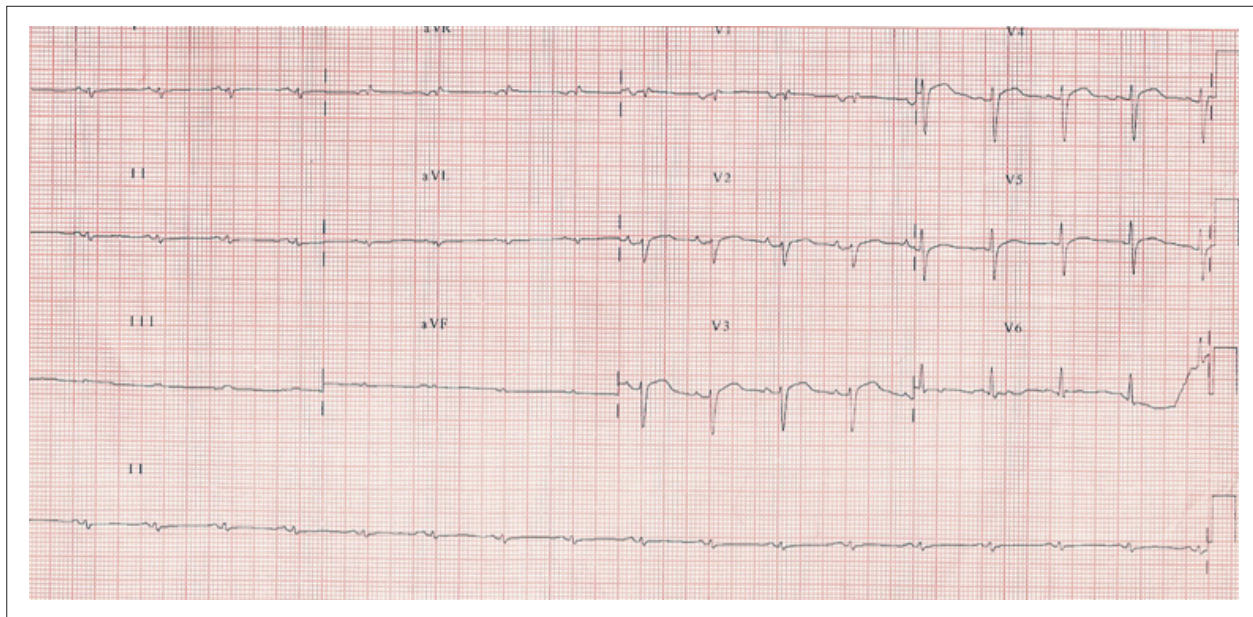


Figura 1 - ECG: sinus rhythm, left atrial overload, indirect right atrial overload signs (Peñaloza-Tranchesí), low voltage of frontal QRS, little progressive R wave of to V_1 a V_4 .

On the night of Jan 27, 2008, the patient presented cardiac arrest under pulseless electrical activity. The patient developed hypotension. A new echocardiogram was done to set aside any likelihood of cardiac tamponade, which revealed left ventricle with concentric hypertrophy of discreet degree and septal hyperrefringency, suggesting an infiltration process and impaired systolic function due to diffused hypokinesia. Right ventricle had a pronounced hypokinesia and discreet to moderate pericardial effusion.

Right thoracic puncture was done and no hemothorax signs were found. Chest radiography after central catheters did not reveal pneumothorax. Around one hour after initial cardiac arrest, new cardiac arrest under pulseless electrical activity, which was irreversible (27 Jan 2008).

Clinical aspects

The case described above refers to 50 years old women with hypotireoidism, who presented progressive dyspnea in the past four months despite heart failure therapy.

Heart failure (HF) constitutes clinical diagnosis through compilation of anamnesis and physical test data¹. The clinical history of HF is characterized effort dyspnea or tiredness. Findings of orthopnea and paroxysmal nocturnal dyspnea are more specific to diagnose this syndrome. It is important to look for risk factors or previous cardiovascular disease. Physical tests may provide more significant inputs to decompensated HF, since sensitivity is low when it is compensated. Alterations are related to congestion or cardiomegaly, besides findings that may suggest the cardiac disease etiology. This way, peripheral edema, tachycardia at rest, pulmonary rales, jugular vein swelling, hepatojugular reflux, hepatomegaly, deviated cerebrovascular accident and accessory crackles should be sought in the preliminary evaluation. Valvar or pericardial

disease may present signs due to the presence of murmurs or pericardial knock, respectively².

The patient presents history of dyspnea related to effort, progressing over time, culminating with symptoms at minimum effort, orthopnea and need for admission. It is important highlighting that there is no description of cardiovascular risk factors nor previous cardiac disease. Physical tests revealed important findings to diagnose the syndrome and data to start reflecting on the HF etiology. Presence of tachycardia at rest is a common finding, but little specific for the diagnosis. There is no description of cerebrovascular accident, given the undisputable diagnostic importance. Report of jugular vein swelling, hepatomegaly and peripheral edema lead us to think in systemic congestion, that is, right heart failure. We should stress that the presence of jugular vein swelling and decreased pulse pressure (PA 90 x 80 mmHg) determine a worse prognosis. The fourth heart sound crackle suggests myocardial diastolic dysfunction. It is worth reminding that severe hepatomegaly may suggest, besides congestion, hepatic tissue infiltration. Preliminary findings also showed bilateral pleural effusion, mainly on the right, as well as it often happens in HF. The effusion may have contributed to dyspnea. The pleural liquid was analyzed at two moments. Upon admission, the first analysis revealed a transudate, confirming effusion secondary to HF. In the second puncture, the liquid has parameters that suggest exudate, but it is worth reminding that at that time the patient was taking diuretic drugs, which may explain the biochemical change of the liquid.

Anamnesis and physical data allow diagnosing HF syndrome. However, clinical history shows data that may suggest the etiology, as there are no reports of hypertension, ischemic disease or cardiovascular risk factors. Physical examinations reveal prevailing findings compatible to right HF.

Upon analysis of complementary tests, chest radiography

Table 1 - Laboratory tests

	9 jan 2008	14 jan 2008	21 jan 2008	27 jan 2008
Hemoglobin (g/dl)	13.8			13.3
Hematocrit (%)	42			39
Mean corpuscular volume (MCV) (fl)	100			98
Leukocytes/mm ³	5500			12100
Neutrophils (%)	64			82
Eosinophils (%)	8			0
Basophils (%)	1			0
Lymphocyte (%)	20			10
Monocytes (%)	7			8
Platelets/mm ³	210000			
Creatinine (mg/dl)	1.81	1.8	3.8	4.98
Urea (mg/dl)	66	83	164	218
Potassium (mEq/l)	4.8			5.8
Sodium (mEq/l)	137			132
TSH (μUI/ml)	normal			6.87
Free T4 (ng/dl)	normal			1
Protein electrophoresis				
Total proteins (g/dl)	6.5			
Albumin (g/dl)	3.7			2.9
Alpha-1 globulin (g/dl)	0.3			
Alpha-2 globulin (g/dl)	0.5			
Beta globulin (g/dl)	1.0			
Gama globulin (g/dl)	1.0			
Urine protein (g/2h)		1.28		
Urine protein (g/l)		6.42		5.7
Serum iron (μg/dl)		35		
Ferritin (ng/ml)		363		
ALT (U/l)				40
AST (U/l)				32
Gamma GT (U/l)				120

confirmed the presence of a huge bilateral pleural effusion, but the cardiac area size was not reported.

Laboratory tests upon admission revealed no consistent alterations in hematological series. Dosing of thyroid hormones revealed that hypothyroidism was compensated. Renal functions was altered since the inception, always with a urea: creatinine ratio > 40, suggesting pre-renal pattern. However, the presence of pathological proteinuria in 24 hour urine suggests renal parenchyma injury. The progressive increase of nitrogenous waste products was possibly related to the use of diuretic drugs during admission.

Initial electrocardiogram revealed signs of biatrial overload, low frontal QRS voltage, besides R wave little progressing from V1 to V4. Among the conditions progressing with low QRS

voltage, we have pericardial effusion, chronic obstructive pulmonary disease and hypothyroidism. Nevertheless, none justify increased cardiac mass detected by transthoracic echocardiogram (TTE). Additionally, no pericardial effusion was found in the TTE, no previous chronic obstructive pulmonary disease, and normal TSH and free T4 clean. On the other hand, the increased myocardial mass as a function of hypertension or hypertrophic cardiomyopathy relates to normal or increase voltage in the electrocardiogram, which was not observed in our case. The presence of hypertrophy in TTE, combined to low electrocardiogram voltage are only found in infiltrative myocardial diseases^{3, 4}.

Amyloidosis in up to 50% of patients may determine to ECG low voltage QRS in limb derivations^{4, 5}. Another frequent usual condition related to this disease is the presence of pseudo-infarction pattern. Both in amyloidosis, and in other heart infiltrative diseases, such as hemochromatosis, sarcoidosis or Fabry disease, conduction disorders are common, often associated to advanced blocking, not observed in this case. Additionally, these diseases also develop with paroxysmal or persistent atrial fibrillation, especially amyloidosis and Fabry disease, not observed either.

Infiltrative cardiomyopathies initially lead to diastolic dysfunction associated to wall hypertrophy, but right ventricle diastolic dysfunction may also occur⁶. In well-developed cases, wall hypertrophy progresses, resulting in restrictive cardiomyopathy, with left ventricular cavity not dilated and small⁶. This pattern, combined with biatrial enlargement are also more frequent in amyloidosis, since in sarcoidosis, especially in hemochromatosis, left ventricular dilation prevails.

Other important factors determined for differential diagnosis with TTE are the presence of scintillating myocardium, and absence of major valvopathy (only valve thickening), found in amyloidosis. Scintillating myocardium is found little sensitive (26% in a series) and cannot be used to eliminate likelihood of amyloidosis⁴. On the other hand, right ventricular dilation is consider to predict amyloidosis and, associated to increased filling pressures, it justifies tricuspid valve insufficiency often present, as in the case reported in this study. Other infiltrative cardiomyopathies, such as sarcoidosis and Fabry disease may develop with valvopathy, especially mitral and aortic valves⁶.

Based on the data presented so far, we consider amyloidosis as the main hypothesis. This is a heterogeneous group of hereditary, inflammatory or neoplasm disorders that result in deposits of amyloid fibrils in several organs, such as heart, kidney and nervous system. Amyloid fibrils are considered low molecule weight protein subunits deriving from normal or aberrant serum proteins⁷. Heart attacks are due to myocardial infiltration of these proteins by different pathogenic mechanisms, becoming clinically apparent when extracellular deposits of amyloid bodies changes normal tissue architecture⁷.

In infiltrative disease, etiology is often confirmed by endomyocardial biopsy. This may happen, for instance, due to Congo red color of amyloid deposits, in amyloidosis; sarcoid granuloma in sarcoidosis; and lamellar bodies in Fabry disease. Nevertheless, endomyocardial biopsy causes impairments and, it often cannot be conducted. Other types of diagnosis should be used. In amyloidosis, this can be done by revealing

amyloid deposits in the histopathological examination of biopsies collected from abdominal fat, rectum or kidney tissue. In this patient, subcutaneous cellular tissue was collected, but revealed no amyloid substance. In retrospective studies, the examination of highly sensitive, especially when several samples are used (it gets close to 100% when at least 4 samples are collected)⁸.

Another revealing test in infiltrative cardiomyopathies is the nuclear magnetic resonance imaging which, in this case, it was not reported, possibly due to the impaired renal function presented, with high likelihood of developing nephrogenic systemic fibrosis.

Summing up, we have the case of a 50-year-old female patient with no previous cardiovascular disease or comorbidity, which evolved to rapidly progressing dyspnea, getting to minimum stress, associated to orthopnea and systemic congestion (hepatic volume enlargement and lower limb edema). She presented non-specific symptoms, however TTE revealed ventricular hypertrophy, ventricular septal hyperrefringency and Doppler revealed restrictive pattern. These findings are compatible to myocardial infiltration processes. Considering the clinical presentation, electrocardiographic and echocardiographic alterations, presence of proteinuria and hepatomegaly, amyloidosis becomes the main diagnosis hypothesis. However, other infiltrative cardiomyopathies may also be investigated due to the symptoms presented and especially because subcutaneous cellular tissue biopsy was negative.

Infiltrative cardiomyopathies are classified under restrictive cardiopathies. These are characterized by rigid myocardial walls associated to non-complacency of one or both ventricles. The left ventricle is more commonly involved, leading to improper ventricular filling and consequent increase of final diastolic pressure⁹.

This group of cardiomyopathies is divided into three distinct classes:

1) myocardial infiltrations, in which the myocardium is infiltrated by an abnormal substance (such as in amyloidosis, sarcoidosis, hemochromatosis and Fabry disease);

2) myocardial fibroses, with fibrous extension over the entire myocardial wall (familial and idiopathic cardiomyopathy);

3) endomyocardial fibroses, with endocardial and subendocardial attacks (endomyocardial fibrosis (EMF), hypereosinophilic syndrome and metastasis of tumor diseases)⁹.

Among myocardial infiltrative diseases, cardiac sarcoidosis should be considered a differential diagnosis.

This is a systemic disease, of unknown etiology, characterized by non-caseous granulomas in any organ, leading to impairment to tissue structures¹⁰.

This cardiac disease is generally done after development of symptoms related to dysfunction of other organs (lung, liver, skin and eyes). However, few patients may suffer heart attacks alone, with no other symptoms of this disease¹¹. Heart attacks occur in up to 30% of patients, although only 5% of them manifest the disease clinically. The disease is characterized by advanced atrioventricular blocks and abnormal wall

thickening¹²⁻¹⁴. Almost all patients present respiratory tract impairments, including hilar lymphadenopathy and interstitial pulmonary infiltrate. Hilar lymphadenopathy attacks 90% of individuals with the disease. Based on the patient's clinical and radiological condition, diagnosis may be suspected, but confirmation should be made from biopsy with demonstration of non-caseous granulomas¹⁵.

Besides cardiac dysfunction, the patient presented hepatomegaly with similar hyperecogenic images and hemangiomas. Sarcoidosis rarely causes major hepatic dysfunction, however a slight increase of hepatic enzymes and major increase of canalicular enzymes may occur, which may often lead to portal hypertension symptoms¹⁰. In the development of the case, considering the diagnosis hypotheses, hepatic or myocardial biopsy could have been conducted, since findings of granulomas close up the diagnosis. Nevertheless, false negative results may occur due because the attack is not homogeneous, mainly in heart diseases¹⁶. What is against the diagnosis of cardiac sarcoidosis in this patient is the presence of septal hyperrefringency in the TTE, as in sarcoidosis, alterations are not specific and may include ventricular aneurism, cavity dilation and wall thickening¹⁷.

Another possible differential diagnosis is the hereditary hemochromatosis. It is characterized as a recessive autosomal disease in which the mutation of gene HFE increases intestinal iron absorption, leading to secondary clinical manifestations upon excessive deposits of iron in the tissues, especially liver, heart, pancreas and hypophysis¹⁸. The heterozygote form of the disease usually clinically comes out during life. This may be found by measuring transferrin saturation (ratio between the concentration of serum iron and total iron-binding capacity)¹⁹. The homozygote form may lead to severe manifestations, generally after 40 years of age. Women may present this disease later than men due to menstrual losses before menopause^{20,21}. The most frequent manifestations are hepatic alterations, lethargy, hyperpigmentation of skin, diabetes mellitus and electrocardiographic abnormalities²². The most common cardiac disorders are ventricular dilation characterized by the development of heart failure and conduction disorders²³. Ventricular hypertrophy is not characteristic, as well as hyper-refringency found in TTE. In the case above, cardiac dysfunction is not typical and serum iron and ferritin levels were normal, which exclude the diagnosis.

While investigating the patient, a less probable diagnosis to be reminded is Fabry disease. This disease consists in deposit of glycolipids connected to chromosome X and is caused by a weak activity of liposomal enzyme Alpha-galactosidase A, leading to subsequent accumulation and deposit of globotriaosylceramide in the tissues²⁴. An important characteristic is that clinical manifestations generally occur before 10 years of age, including skin lesions and peripheral neuropathy, although some population-tracking studies report later inception (after 40 years of age)²⁵. In relation to cardiac attacks, this may lead to major ventricular hypertrophy, conduction disorders, coronary arterial disease and aortic and mitral valve failure. However, the main symptoms include palpitations, chest pain and dyspnea. Major ventricular failure symptoms are uncommon. In some mutations^{25,26} the presence of cardiac attacks is reported. This explains why the disease is investigated in patients with ventricular

hypertrophy with no apparent cause.

Initial investigation may be made with demonstration of low alpha-galactosidase A levels and diagnosis is confirmed with endomyocardial biopsy revealing concentric lamellar bodies in the sarcoplasm of cells²⁴. In a less invasive way, TTE may distinguish myocardial hypertrophy found in the Fabry disease from other forms of ventricular hypertrophy by revealing endocardial and subendocardial hyperechoic thickening due to glucolipid deposits. Concomitantly, we observe a parallel hypoechoic thickening along the entire myocardial surroundings. This alteration is called binary appearance of the ventricle endocardial edge²⁷. In the case described, the echocardiographic pattern is not similar to the one described for the disease, as well as there is no known family history of diseases connected to chromosome X or family history of ventricular hypertrophy, which are considered highly relevant to investigate the disease²⁸.

Concerning endomyocardial fibrotic diseases as a differential diagnosis for this case, we should remember the endomyocardial fibrosis, an undefined etiology entity prevailing in the tropical zone²⁹.

It is characterized by a fibrotic involvement of the endocardium and adjacent myocardium, apex and ventricular inflow. The fibrotic process often affects papillary muscles determining atrioventricular valve dysfunction. This condition generates ventricular filling restriction, causing the clinical manifestations and hemodynamic disorders suggesting the disease. It also affects both sexes. It has been reported to have affected individuals from 4 to 70 years of age, although it prevails in children and young adults²⁹.

Clinically speaking, patients with endomyocardial fibrosis may present right, left or both HF, depending on the degree of ventricular involvement. One or both atrioventricular valves may often present failure, due to severe involvement of papillary muscles. The inception of the disease is deceitful. The disease seldom stabilizes, leading to progressive myocardial failure.

A major concern in this disease is that TTE often detects ventricular apex obliteration. Other concerns include dilated atrium, with normal or slightly dilated ventricular cavities. Thickened posterior wall or anterior ventricular septum in patients with left or right ventricle affected, respectively, may also be found²⁹. TTE may reveal associated pericardial effusion. The patient described in this case did not present TTE compatible to the classical endomyocardial fibrosis description, due to absence of ventricular apex obliteration, besides diffuse septal thickening suggesting infiltrative disease. Age range little compatible to this condition is also a concern.

Although the patient was under HF therapy, symptoms persisted, and progressive worsening of renal functions and hypotension were observed. The patient was transferred to the ICU, where she had a cardiorespiratory arrest (CRA), under pulseless electrical activity (PEA). Generally speaking, possible causes of CRA under PEA are: hypoxemia, hypovolemia, hypothermia, hyperkalemia, acidosis, hypoglycemia, acute myocardial infarction, pulmonary thromboembolism, pneumothorax, tamponade, drugs, trauma. Potassium measured on CRA was 5.8 mg/dL, but no description of blood gas measurements or blood glucose. Chest radiography did not

reveal pneumothorax, nor other complications deriving from invasive medical procedures. TTE revealed existing alterations, rejected tamponade, but revealed major right ventricular dysfunction described as moderate in previous TTE. Then, we considered pulmonary thromboembolism progressing to shock as the main cause of death. However, although hyperkalemia is not as important, it cannot be disregarded as a decisive factor. (Dr. Odilson Marcos Silvestre, Dr. Henrique Barbosa Ribeiro, Dr. Leonardo Jorge C. de Paula, Dr. Sérgio Ricardo V. Macedo)

Diagnosis hypothesis: Systemic amyloidosis with hepatic, renal and cardiac impairments, determining right and left myocardial dysfunction; cardiogenic shock; pulmonary thromboembolism.

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Necropsy

Necropsy revealed light cardiac wall thickening and left ventricular dilation, and moderate right ventricular dilation (Figure 2a). The entire myocardium was hardened, "rubber-like" and brownish-yellowish colored. Discreet yellowish granules were observed on the endocardial surface of the left atrium (Figure 2b, c and d). Congestive heart failure signs were also observed, such as: cavity effusions (hydrothorax - with 1.560 mL to the right and 1.200 mL to the left, and hydroperitoneum - with 960 mL, of yellow citrine liquid), as well as chronic passive congestion in lungs and liver.

Hystological examination of the myocardium revealed plenty of amorphous and pinky deposits within the sarcolemma of myocardiocytes and in the interstice around these, found positive due to the Congo red color (Figure 3), with bottle-green or apple-green colored refringency through polarized light, consistent with amyloid deposits (Figure 4). Amyloid deposits were observed in vessels and plain muscles of several organs, such as: lungs (in alveolar septa and vessels); spleen (in periarteriolar areas and close to follicles); kidneys (in vessels); intestines (plain muscles of walls and vessels); thyroid (vessels).

The bone marrow was investigated for plasma cell dyscrasia. Severe infiltration of plasma cells, moderately well-distinguished totaling around 80% of cell elements. Immunohistochemical study with antibodies for kappa and lambda light chains revealed lambda monoclonal profile of plasma cell infiltration in the bone marrow (Figure 5). Emboli of plasma cells were observed in lung vessels, which could suggest leukemization. Additionally, kidneys presented the alterations described in cases of multiple myeloma, with diffuse and finely granulose renal surface and, in histology, various hyaline or finely granulose cylinders, in renal marrow tubules. These findings also included alterations of laboratory tests (normocytic normochromic anemia, increase of creatinine and proteinuria).

Other minor findings for this condition were a

Anatomopathological Session

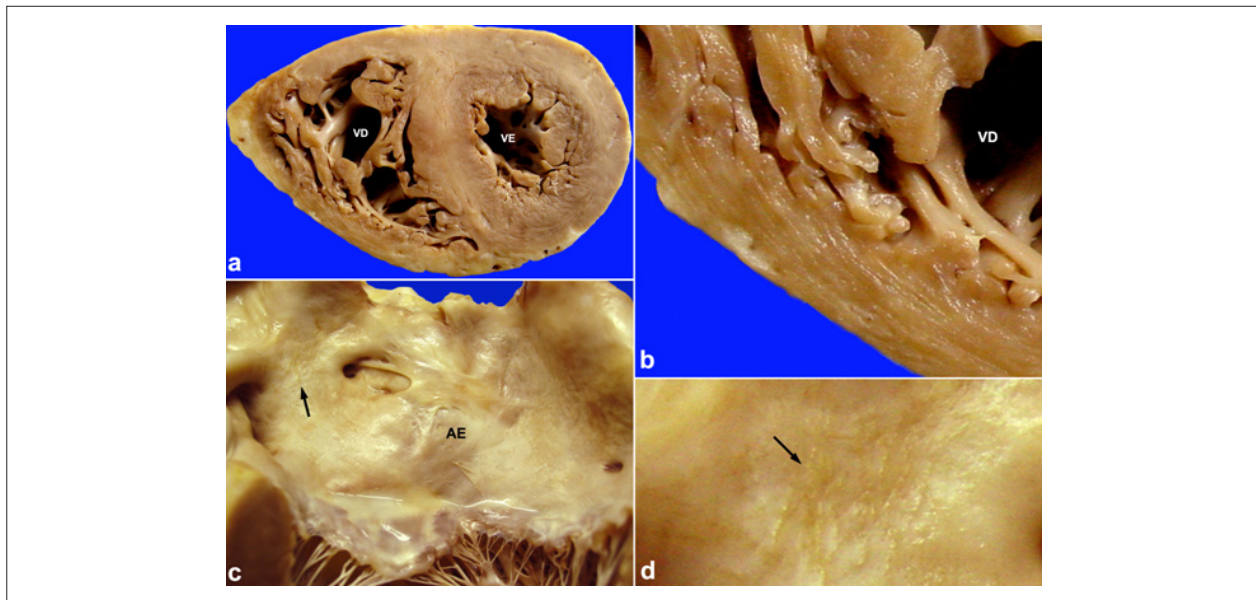


Figure 2 - Heart images. In (a), we observe increased muscles and light dilation on left ventricle (LV) cavity and moderate dilation on right ventricle (RV). Myocardium presents a brownish-yellowish color, better observed in detail (b). The left atrium (LA) presented yellowish grooves and granules on the endocardium surface, suggesting amyloid deposits. The arrow in (c) indicates the area where this aspect is evident, which is shown in detail through the arrow in (d).

hepatic hemangioma, with 1.5 cm and discreet aortic atheromatosis.

As a terminal cause for the death, we observed right pulmonary thromboembolism, with thromboemboli in lobe artery, with a large hemorrhage area on the right lower lobe, and consequent cardiogenic shock, with cerebral edema (1240g), with slight convexity flattening and hernia of cerebellar amygdalae.

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Anatomical-pathological diagnoses:

Malignant neoplasm of lambda plasma cells in the bone marrow, associated to the other anatomical-pathological and laboratory alterations, consistent with diagnosis of multiple myeloma, including primary amyloidosis or systemic AL amyloidosis, with heart deposits (severe), lungs, spleen, kidney, digestive tract and thyroid; right pulmonary thromboembolism; cardiogenic shock; hepatic hemangioma; light aortic atherosclerosis.

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Comments

Amyloidosis is associated to multiple diseases involving deposits of proteins with similar appearance (similar physical nature), with variable structural and functional burst of the organ damaged by the deposits^{30,31}. In electronic microscopy, X-ray crystallography and infrared spectroscopy, the fibril structure is identical in all types of amyloidosis. The amyloid is composed of fibril proteins (95%) and glycoproteins (5%). However, it differs as to its chemical nature, which included 15 different biochemical forms. The three most common forms are: AL, AA and A β ³¹.

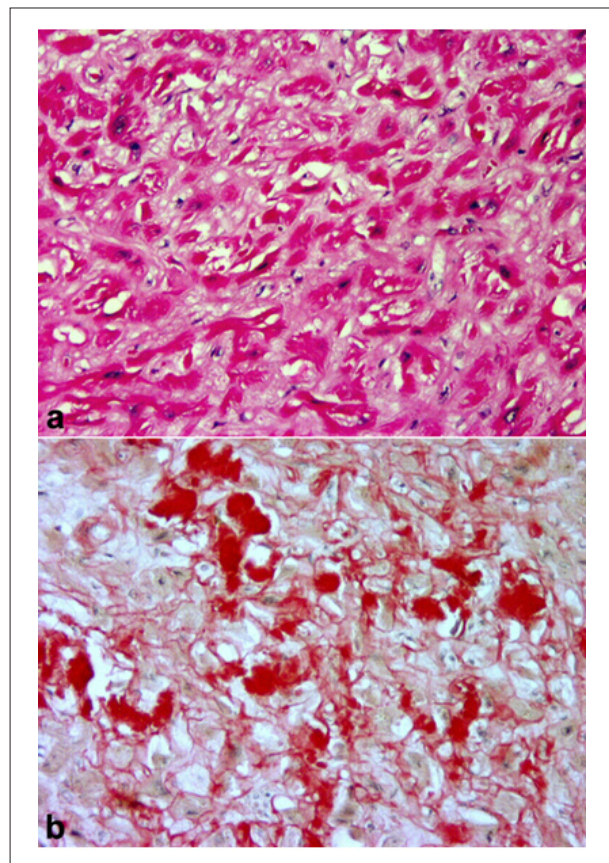


Figure 3 - Myocardial histology images. In (a), we observe amorphous and pinkish material deposits, suggesting amyloid, within the sarcolemma of myocytes and in the interstice around these. In (b), the red color corresponds to the positive Congo red reaction, confirming myocardial amyloid deposits [Haematoxylin & eosin in (a) and Congo red in (b); 5X objective in both images].

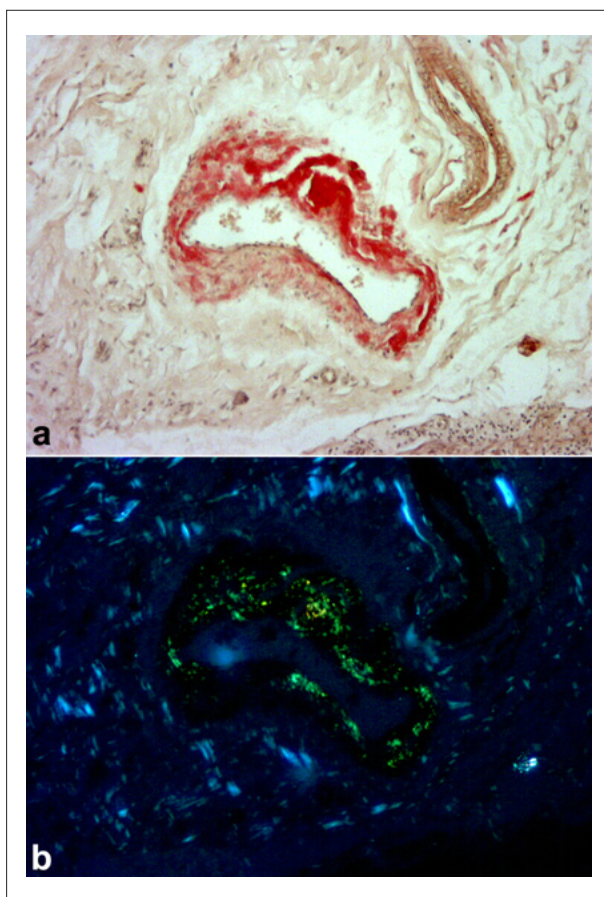


Figure 4 - Images of a gastrointestinal tract vessel. In (a), the Congo red reveals amyloid deposits on the vessel wall (red color). In (b), we observe the apple-green or bottle-green color characteristic of Congo-red colored amyloid deposits observed through polarized light. [Congo red; 40X objective in both images]

The most common amyloidosis, the AL form (light chain amyloid), is composed of light chain fragments of immunoglobulin. It occurs in 5 to 15% of patients with multiple myeloma and in patients with no myeloma: the latter would have an increase in the number of plasma cells in the bone marrow (plasma cell dyscrasia), which are called monoclonal gammopathies, dysproteinemias or paraproteinemias. Therefore, AL amyloidosis may be present in malignant, benign or pre-malignant conditions (as in the described in this paper). In this type, mature lymphocyte B in monoclonal proliferation produces a single type of immunoglobulin deposit. In primary amyloidosis, around 80% of patients have only the monoclonal immunoglobulin, most of which of lambda type. Bone marrow plasmocytosis is modest, and 20%, multiple myeloma^{30,31}.

The AA form relates to a serum amyloid associated protein derivate produced in the liver in order to provide support to phagocytosis by macrophages. It occurs in combination with chronic inflammatory diseases, such as lepromatous leprosy, tuberculosis, osteomyelitis, bronchiectasis, and rheumatoid arthritis, which may last for years³¹.

The A β form is found in cerebral lesion (plaques) and in Alzheimer disease vessels. In addition to that, the ATTR amyloidosis (deriving from transtirretin or pre-albumin), a

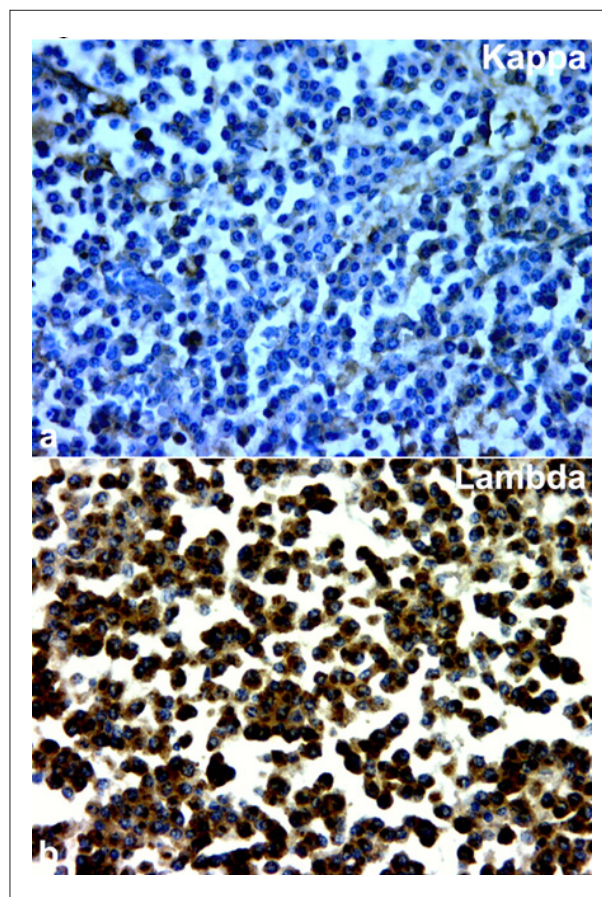


Figure 5 - Histology of iliac bone marrow. Hematopoietic tissue was greatly replaced with plasma cells, which are observed in these images, which, in (a), were negative for kappa light antichain antibody and, in (b), were positive for lambda light antichain antibody, revealing the monoclonality (brown color corresponds to positive). (Immunohistochemical reactions for light chains; 40x objective in both images).

plasmatic protein that carries tiroxin and retinol (vitamin A), which is present in genetically determined disorders (family-derived) and in deposits found in elderly hearts (senile systemic amyloidosis), among other forms that will not be detailed in this study³¹.

The amyloidosis diagnosis depends on the morphological identification of amyloid in proper tissue samples observed in optical microscopy^{31,32}. In clinical suspects, the first step would be the demonstration of amyloid deposits, and abdominal fat biopsy^{33,34} has been used and proven positive in 85% of cases of amyloidosis AL³³. Once the suspected deposit is detected, which is characterized by amorphous material and clear eosinophilic stain on the tissue, it should be analyzed with Congo red color, ideally in 10 μ m thick cuts. If this color is positive, it will result in a red tonality, under normal light, and apple-green or bottle-green under polarized light. Then, the amyloid type should be investigated according to the algorithm established³³. If no family history is reported, type AL is the major suspect, since it comprises most cases. Thus, the investigation carries on by seeking plasma cell dyscrasia through protein survey by immunofixation of blood and urine,

besides bone marrow biopsy. Immunofixation replaces the immunoelectrophoresis technique as it is more sensitive and faster, combines electrophoresis and immunoprecipitation techniques which, through antigen-antibody interaction, increases the capacity to identify specific immunoglobulin upon use of specific antibodies. Bone marrow biopsy should be studied with employment of immunohistochemistry for kappa and lambda light chains. If studies are proven negative, the investigation should be directed to the other forms³³. Determining the type of amyloid is necessary, since the therapy, besides providing support according to the organ

affected, should be directed to the root cause to reduce or stop amyloid deposits^{33,35}. Inhibition of amyloid fibrils and anti-amyloid drugs with proteolytic action are two other therapy targets under study^{34,35}.

Prognosis is reserved in generalized AL amyloidosis, with survival of 1 to 2 years³³. Combined use of autologous bone marrow transplantation and chemotherapy are two therapies used to improve this condition^{4,35}. In reactive systemic amyloidosis (AA), prognosis depends on the underlying disorder³³.

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