A 55-year-old man, a retired bricklayer, born in Itapetim (State of Pernambuco, Brazil), sought medical care due to shortness of breath (11/04/2005). Three years earlier, he had started to develop progressive worsening of dyspnea, which was initially triggered by severe exertion. One year earlier, dyspnea started to be triggered by moderate exertion and was associated with tachycardic palpitations. The patient sought medical care in a primary health care unit where he was prescribed medications, the names of which he could not recall. He improved after the use of these medications. He had been previously diagnosed with Chagas disease.

The patient was receiving carvedilol 3.125 mg bid, digoxin 0.25 mg, spironolactone 25 mg, acetylsalicylic acid 100 mg, and hydrochlorothiazide 12.5 mg in combination with amiloride 1.25 mg daily.

Physical examination revealed weight of 74.8 kg, height of 1.64 m, body mass index of 27.8 kg/m², pulse of 78 beats per minute, and blood pressure of 110/80 mmHg. Lung examination was normal. Heart examination revealed normal heart sounds, regular rhythm, no extra sounds, clicks or murmurs. Abdominal examination was normal. There was no leg edema.

Electrocardiogram (11/01/2005) showed sinus rhythm and low-amplitude R-waves in limb and precordial leads; intraventricular conduction abnormality; left ventricular; and atrial overload (Figure 1).

Chest radiography showed grade 3/4 cardiomegaly.

A diagnosis of heart failure secondary to chagasic cardiomyopathy was made.

Medication adjustment was made with discontinuation of acetylsalicylic acid and of the combination hydrochlorothiazide/amiloride, and increase in the carvedilol dose to 6.25 mg bid; enalapril was added at 10 mg bid.

A test for detection of anti-Trypanosoma cruzi antibody was positive (11/3/2005).

Radiocardiography (gated blood pool) (6/14/2006) with ⁹⁹ᵐ-Tecnetium-labeled red blood cells showed bilateral abnormal rhythm of ventricular clearance of the tracer and bulging of the main pulmonary artery. The mean pulmonary transit time was longer than 20 seconds. The right atrium and ventricle were enlarged. There was marked diffuse right ventricular hypokinesia. The left ventricle was significantly enlarged and there was marked diffuse hypokinesia and dyskinesia in the left ventricular inferior apical region. Motion of the left ventricular inferior apical region was in phase opposition in relation to the other walls. The left ventricular and right ventricular ejection fractions were estimated at 13% and 24%, respectively.

Laboratory tests (07/13/2006) revealed: hemoglobin 18.1 g/dL, hematocrit 54%, MCV 100 fl, MCHC 34 g/dL, 5.4 x 10⁶ erythrocytes per mm³, 6.9 x 10⁹ leukocytes per mm³ (neutrophils 72%, eosinophils 2%, lymphocytes 18%, monocytes 8%), sodium 137 mEq/L, potassium 5.1 mEq/L, BUN 82 mg/dL, creatinin 1.1 mg/dL, aspartate aminotransferase 36 U/L, alanine aminotransferase 56 U/L, uric acid 7.3 mg/dL, albumin 3.7 g/dL, total bilirubin 1.36 mg/dL (direct 0.68 mg/dL, indirect 0.68 mg/dL), prothrombin time 19.3 sec (INR 1.45), 24-hour proteinuria 0.14g (normal up to 0.15). Stool examination for parasites (Hoffman, Rugai) was negative; carcinoembryonic antigen was 2.8 ng/mL (reference value up to 5.0 ng/mL).

The patient underwent cardiac catheterization (8/3/2006) which showed moderate pulmonary hypertension (Table 1), however without any obstructive lesions in coronary arteries.

Pulmonary ventilation-perfusion scintigraphy (9/12/2006) was consistent with a low probability of pulmonary embolism.

In 10/06/2006, the patient complained of tiredness on exertion and leg edema. The diuretic dose was increased with furosemide 80 mg daily in addition to the medication he was already receiving.

In 11/03/2006, BUN was 81 mg/dL, creatinin 1.55 mg/dL, and serum potassium 4.9 mEq/L.

In one of his outpatient visits (12/04/2006), he complained of shortness of breath, episodes of dizziness and presyncope 15 days earlier. He also complained of leg and abdominal edema. He was receiving hydralazine 25 mg bid, furosemide 40 mg bid, as well as spironolactone, carvedilol, enalapril and digoxin. He was advised to adjust his diet, activity and medication; the diuretic dose was reduced.

Echocardiogram (01/03/2007) showed: aorta 32 mm, left atrium 52 mm, right ventricle 30 mm, interventricular septum 8 mm, left ventricular posterior wall 8 mm, left ventricular...
Table 1.

<table>
<thead>
<tr>
<th>Pressures (mm Hg)</th>
<th>Systolic</th>
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<th>End-diastolic</th>
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<tr>
<td>Left ventricle</td>
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<td>Pulmonary vascular resistance (U Wood)</td>
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</table>

Figure 1 - ECG: sinus rhythm and low-amplitude R-waves in the frontal plane and precordial leads; intraventricular conduction abnormality; left ventricular and atrial overload.

Diastolic diameter 76 mm, left ventricular systolic diameter 66 mm, left ventricular ejection fraction (Teichholz) 27%. Doppler imaging study showed flow patterns consistent with a restrictive pattern, which reverted after Valsalva maneuver.

The heart valves were considered normal. The pulmonary artery systolic pressure was estimated at 55 mmHg.

The symptoms improved after the medication adjustment made in December (01/12/2007).

Laboratory assessment in the follow-up showed: fasting plasma glucose 106 mg/dL (09/18/2007), B-type natriuretic peptide 1021 pg/mL (reference value: < 100 pg/mL), cholesterol 220 mg/dL, HDL-cholesterol 39 mg/dL, LDL-cholesterol 157 mg/dL, TSH 2.87 mIU/mL, free T₄ 1.7 ng/dL, blood glucose 106 mg/dL, glycosylated hemoglobin 6.1%, CA 19.9 2.6 U/mL (reference value up to 37 U/mL) (10/29/2007).

Abdominal ultrasonography (05/12/2008) showed atheromatous aorta and hyperechoic nodular lesions in the liver, considered as consistent with hemangiomas.

In 06/03/2008, the patient developed cough with yellow sputum, in addition to dyspnea. He sought medical care in a Primary Health Care Unit and was prescribed levofloxacin 500 mg once a day. There was clinical improvement.

He later sought medical care again (07/03/2008) due to persistent chest pain for two days, which worsened with deep breath or cough and radiated to the back; he also presented bloody sputum.

He was receiving carvedilol 50 mg, enalapril 40 mg, digoxin 0.125 mg, furosemide 40 mg, hydrochlorothiazide 25 mg, spironolactone 25 mg, and omeprazol daily.

Physical examination revealed pulse of 80 beats per minute and blood pressure of 80/40 mmHg. The rest of the physical examination was negative for other diagnostic clues.

Electrocardiogram performed in 07/03/2008 did not show any significant change in relation to the previous test.
Chest radiography (07/03/2008) showed an image suggestive of diffuse reticular-alveolar infiltrate in the lungs. CT scan of the chest (07/03/2008) showed mediastinal vascular structures of normal diameter and regular contours; cardiomegaly; mediastinal lymph nodes smaller than 10 mm; sparse calcified micronodules in both lungs; non-calcified nodule with spiculated borders measuring 1.6 x 1.4 cm in the medial-basal segment of the RLL; diffuse micronodules with centrolobular distribution in both lungs; thickened interlobular septae in the right lung; opacity with ground-glass attenuation predominantly in mid and basal portions of the right lung; and consolidation in the right lung base.

The diagnoses of lymphangitis, stasis or sarcoidosis were postulated.

Sputum culture for mycobacteria and acid-fast bacilli test (07/04/2009) were both negative.

The patient received intravenous clarithromycin 500 mg every 12 hours and intravenous ceftriaxone 1 g every 12 hours, in addition to the cardiovascular medication he already used. Dobutamine was also administered.

In 07/07/2008, he presented a clinical picture described as acute pulmonary edema, which improved with the use of diuretics, non-invasive ventilation and vasodilators.

The next day (07/08/2009), the patient suffered cardiac arrest with pulseless electrical activity which failed to respond to resuscitation efforts.

Comments – InCor chest radiologist

In the CT scan of the chest performed without intravenous iodine contrast medium, a non-calcified pulmonary nodule with lobulated contours was identified in the right lower lobe, whose tomographic aspect was suggestive of primary neoplasia (Figure 2). In the right lung, there was associated peribronchovascular and septal interstitial thickening, sometimes with smooth aspect and with a micronodular pattern in some regions, which led to the possibility of carcinomatous lymphangitis (Figures 2 to 4). Worthy of note were also multiple small non-calcified nodules disseminated in all lung fields, which, in this clinical context, are consistent with secondary lesions (Figures 2 to 4). The tomographic views also revealed sparse foci of pulmonary consolidation with pleural base bilaterally; they were surrounded by ground-glass opacities and predominated in the basal segments of the right lower lobe (Figure 5). They were consistent with infarct areas and pulmonary hemorrhage in the clinical setting of acute thromboembolism. (Dr. Rodrigo Caruso Chate)

Clinical aspects

The patient is a 55-year-old male who, in November 2005, sought medical care due to dyspnea which had worsened progressively for three years and was associated with tachycardic palpitations; he had serologic tests positive for Chagas disease. Physical examination was normal; electrocardiogram (ECG) showed left bundle branch block and low-amplitude R-waves; chest radiography showed enlarged cardiac silhouette (grade 3/4 cardiomegaly), consistent with heart failure whose probable cause was Chagas disease in its chronic dilated cardiomyopathy form. He used low doses of carvedilol in addition to digoxin, acetylsalicylic acid, spironolactone, hydrochlorothiazide, and amiloride. Medication adjustment was made with the introduction of angiotensin-converting enzyme inhibitor (enalapril) and follow-up was started.

Some considerations regarding the etiology of heart failure can be made. Chagas disease in its chronic form is characterized by diversity. There are asymptomatic patients in the indeterminate form, asymptomatic patients with electrocardiographic abnormalities, and symptomatic patients with varying degrees of ventricular dysfunction. There are severe atrioventricular and intraventricular conduction disturbances, those with thromboembolic phenomena, and with varying degrees of ventricular arrhythmias1-4. Conduction abnormalities are, undoubtedly,
The prognosis of the chronic form of Chagas cardiomyopathy is related to the degree of ventricular dysfunction as assessed by left ventricular ejection fraction (EF); the lower the EF, the worse the prognosis (like in other cardiomyopathies). There is also a correlation with the functional class and oxygen consumption. Additionally, the disease is more aggressive in men, and the reason for this remains unknown.

From the first visit, the analysis of this patient’s ECG and chest radiography showed severe myocardial impairment due to Chagas disease, as evidenced by the presence of interventricular conduction disturbance, low-amplitude R-waves, and significantly enlarged cardiac silhouette. These findings, together with the patient’s symptoms, lead to the presumption of severe dilated cardiomyopathy.

Radiocardiography performed in the follow-up showed severe left ventricular hypokinesia (EF = 13%), with dyskinesia of the inferior-apical region, as well as right ventricular hypokinesia (EF = 24%), with bulging of the main pulmonary artery, thus confirming severe systolic dysfunction with secondary pulmonary hypertension (PH). Among the laboratory tests, the high hemoglobin level (18 g/dL) is worthy of attention, and may be justified by pulmonary hypertension; also, a mildly decreased renal function was possibly due to the use of diuretics or to the low cardiac output.

The patient underwent cardiac catheterization, whose pressure measurements showed moderated pulmonary hypertension with no obstructive coronary lesions, thus ruling out coronary artery disease. PH was partially reverted with nitroprusside and oxygen mask. Pulmonary vascular resistance dropped from 6.3 U Wood to 2.2 U Wood. To further investigate PH, pulmonary perfusion scintigraphy was performed, showing a low probability of pulmonary embolism.

According to thromboembolic complications, especially pulmonary, these can be the first manifestation of the disease. Regional deficits may determine thrombosis, even with preserved global function. Patients at a higher risk are those with severe myocardial dysfunction, atrial fibrillation, LV apical lesion, presence of intracavitary thrombi, and previous embolism.

During the follow-up, 11 months after the first visit, the patient presented worsening of the functional class, and the diuretic dose was increased. His renal function slightly worsened. Two months later, in another visit, he presented symptoms of low cardiac output, with dizziness and presyncope.

In this phase of the disease, we applied the score elaborated by Rassi et al for the assessment of the risk of death in patients with Chagas disease, which takes into consideration functional classes III and IV (NYHA) (5 points); evidence of cardiomegaly on chest radiography (5 points); LV systolic dysfunction on echocardiography (3 points); non-sustained ventricular tachycardia on Holter monitoring (3 points); low-voltage QRS on ECG (2 points); and male gender (2 points). This patient’s score was 17, which classified him in the high-risk group, with 63% mortality in five years and 84% in 10 years. Therefore, this patient was progressing to stage-D heart failure, and the possibility of cardiac transplantation could have been considered.
Cardiac transplantation is indicated in symptomatic patients in functional class III or IV (NYHA) during drug therapy properly optimized, with life expectancy of less than one year, and no possibility of other medical or conventional surgical treatment.

Pulmonary hypertension is a factor that precludes cardiac transplantation and represents the main cause of RV dysfunction of the graft in the immediate postoperative period. Pulmonary vascular resistance higher than 2.5 U Woods has been pointed out as an important risk factor, considering that mortality progressively increases above these levels. Thus, in the present case, there was no contraindication for cardiac transplantation.

In January 2007, the patient underwent echocardiography, which showed significant left atrial enlargement (52 mm); LV diastolic and systolic diameters of 76 mm and 66 mm, respectively; EF of 27%; and pulmonary artery systolic pressure of 55 mmHg.

In the third follow-up visit, after diuretic reduction, there was improvement of the symptoms; with the purpose of a preoperative assessment for a possible transplantation, the patient underwent a series of tests. One of the results, a BNP level of 1021 pg/mL, suggested advanced decompensated heart failure despite the optimized therapy.

Abdominal ultrasonography showed atheromatous aorta and hypeerechoic nodular lesions consistent with hemangiomas.

In June 2008, the patient developed pneumonia and was treated with levofloxacin, with subsequent improvement. One month later, he developed persistent chest pain for two days, which worsened with deep breath and cough and radiated to the back; he also presented hemoptysis and hypotension. Electrocardiogram did not show differences in relation to the previous test; chest radiography showed an image suggestive of diffuse reticular-alveolar infiltrate in both lungs.

At that moment, the diagnostic hypotheses were alveolar hemorrhage secondary to pulmonary hypertension, complicated bronchopneumonia, tuberculosis and pulmonary thromboembolism (PTE). The latter should always be included in the differential diagnosis of this type of patient seen in the emergency room.

The clinical diagnosis of PTE is particularly difficult for two reasons. First, the clinical findings depend both on the size of the embolus and on the preexisting cardiopulmonary status. Second, the signs and symptoms of PTE are not specific of this disease. Among the symptoms, dyspnea occurs in approximately 75% to 85%, pain with breathing in approximately 65% to 75%, and cough in 53% of the patients with PTE.

In a study assessing cardiac thrombosis and embolism in 111 patients who died of chronic Chagas heart disease in the Instituto do Coração, embolism was observed in 60% of them; of these, 65% had pulmonary embolism. Systemic embolism was found in 38% of the cases, and the renal region was affected in 70% of the episodes. We can conclude that the incidence of thrombosis and embolism is high among patients with severe myocardial dysfunction, and there is a relationship between both conditions, although not absolute.

This patient underwent CT scan of the chest to elucidate the radiographic findings and clarify the diagnosis.

CT scan of the chest showed mediastinal lymph nodes; sparse calcified micronodules in both lungs; non-calcified nodule with spiculated borders measuring 1.6 x 1.4 cm in the medial-basal segment of the right lower lobe; interlobar septal thickening in the right lung; opacity with ground-glass attenuation, predominating in the mid and basal portions of the right lung; and consolidation in the right lung base.

In view of these findings, the following hypotheses were made: carcinomatous pulmonary lymphangitis, stasis or sarcoidosis. The hypothesis of tuberculosis was ruled out because of negative sputum cultures and acid-fast bacilli test.

Carcinomatous lymphangitis more commonly originates from primary breast, lung, stomach, colon, prostate, and pancreas neoplasms. Differential diagnosis should be made with other diseases which preferably disseminate via the lymphatic vessels, such as sarcoidosis, lymphomas, leukemias, paracoccidioidomycosis, Kaposi’s sarcoma, diffuse pulmonary lymphangiomatosis, and lymphangiectasias. The aspect most frequently observed in carcinomatous lymphangitis is interlobular septa and bronchovascular sheath thickening, and this can be smooth or nodular. Other common findings are nodules distributed along the lymphatic vessels (pleural surface, bronchovascular sheaths, interlobar septa and centrolobular region). Pleural effusion is a frequent association. An important characteristic is the preservation of the normal pulmonary architecture, with no signs of parenchymal distortion (fibrosis). In patients with myocardial dysfunction, particularly right ventricular dysfunction, the differential diagnosis with congestion is difficult to be made by means of imaging studies. The basic histological findings in carcinomatous lymphangitis are interlobular septal and peribronchovascular interstitial thickening due to neoplastic cell infiltration inside the lymphatic vessels. However, it should be considered that interstitial thickening can also result from fibrosis associated with desmoplastic reaction, from edema caused by lymphatic obstruction or congestion, or still from a combination of all these factors.

Sarcoidosis is a systemic disease of unknown cause, characterized by noncaseating granulomas. It affects women more frequently than men, and manifests in the third or fourth decades. Although it can affect any organ, and its morbidity and mortality are mainly related to the pulmonary involvement, which is present in 80% to 90% of the patients. The nodular pattern is the most frequently seen in pulmonary sarcoidosis. The nodules are usually small and are distributed along the lymphatic vessels; they are located in the peribronchovascular bundles, interlobar septa, subpleural centrolobular regions, and along the fissures. Cavitary or large nodules, sometimes suggesting neoplasia, may be found in 15% to 25% of the cases. Other tomographic findings in sarcoidosis are ground-glass opacities, parenchymatous opacities, air trapping, fibrosis and bronchiectasias. The diagnosis requires histological demonstration of noncaseating granulomas on biopsy.
Chronic pulmonary congestion due to increased hydrostatic pressure may lead to alterations in the CT scan of the chest, like bronchi with thickened walls and apparent increase in the diameter of central and peripheral pulmonary vessels. With the persistence of increased interstitial pressure, the image of the interlobular septa — which are thickened due to fluid infiltration, becomes noticeable. Another aspect found in interstitial edema is the presence of ground-glass opacities.\(^{1,12}\)

In view of the exposed, and based on the description of the CT scan of the chest, none of the three hypotheses mentioned was ruled out, since they require histological data.

During the follow-up, the patient received antibiotics and dobutamine again. On July 7th, the patient developed pulmonary congestion, which improved with clinical measures. The next day, he suffered a cardiopulmonary arrest (CPA) in pulseless electrical activity (PEA); resuscitation efforts were unsuccessful.

Considering the hypothesis for CPA in PEA, and according to the considerations previously made, we conclude that the cause of death was pulmonary thromboembolism. (Dra. Angela Cristina Materia Bolonhez and Dr. Murilo Capreti Silva)

Main diagnostic hypothesis: Pulmonary Thromboembolism; Dilated Chagas Cardiomyopathy.

Other hypotheses: Carcinomatous pulmonary lymphangitis secondary to primary lung neoplasia; chronic pulmonary congestion; and, less likely, pulmonary sarcoidosis.

Necropsy

The morphological examination of the heart revealed enlarged globoid heart (Figure 6A), with areas of pericardial thickening (“milky spots”), and disseminated focal chronic myocarditis (Figure 6B), which are some of the classic characteristics of Chagas cardiomyopathy. However, tapering of the left ventricular apex was not observed. Likewise, Trypanosoma cruzi nests were not detected (as usually occurs, in fact).

Thromboembolism was observed in the kidney and lungs (Figure 7), with recent infarction. The involvement of these two organs was the final factor triggering the death of the patient. The source of the emboli was not found.

The lungs also presented adenocarcinoma with bilateral miliary dissemination to the organ itself (Figure 8A and B). It can not be ruled out that this disease had influenced thrombus formation, because vessels with neoplastic involvement were observed in the regions of edema and infarction. The existence of a clot in a renal vessel leading to infarction, without neoplasia, speaks against this possibility; however, even in this location, thrombosis can be a paraneoplastic manifestation. (Dr. Paulo Sampaio Gutierrez)

Main diagnoses: 1) Chagas disease, chronic cardiac form; 2) Pulmonary adenocarcinoma with miliary dissemination.

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

Comment

The clinical picture of this patient with Chagas disease, chronic cardiac form, was complicated by the association with pulmonary adenocarcinoma.

The association of Chagas disease with neoplasia is uncommon. Among the 240 autopsies with this infectious disease performed at the Instituto do Coração, other cases of this association included one male patient with mesothelioma, two women with clinical history of previous treatment of breast cancer, and one patient with lymphoma who had previously undergone cardiac transplantation. Anyway, this population is not representative. It is very likely that Chagas disease, especially in its indeterminate form, is more usually a secondary finding in patients with malignant neoplasias than otherwise, as represented by our sample.

Development of neoplasms is described in patients undergoing transplantation. Surveys conducted in Brazil showed that among heart transplanted patients, the incidents of neoplasias was higher in those whose transplantation was...
motivated by Chagas disease; however, there were no reports of pulmonary neoplasias. Studies on the association between Chagas disease and neoplasias are scarce. Almeida et al reported that the literature on the theme shows that this is a controversial issue, and that no increase or reduction in the frequency of malignant neoplasias was verified among patients with chronic Chagas disease. They also verified that malignant neoplasias do not interfere in the short-term course of the heart disease. There are reports on the association of colon carcinoma with chagasic megacolon; nonetheless, some authors consider that the latter is perhaps a protective factor against cancer. As regards megaesophagus, there seems to be a certain agreement on the relationship between the diseases, even though the incidence found for cancer in chagasic megaesophagus is variable, with rates from 3.9% to 10% being reported.

References