

## Case 3 - Congestive Heart Failure in Male with Systemic Sclerosis

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71 year-old Caucasian male, resident of Campinas – SP, diagnosed with diffuse systemic sclerosis, with clinical condition initiated by skin stiffening in lower limbs for seven months, which spread three months ago to the upper limbs (hands and forearms) and, one month ago, to chest and abdomen; in addition to confirmatory laboratory exams, such as the research of anti-nuclear factor reagent in 1:640 titration with dense fine speckled pattern and anti-topoisomerase antibodies I (Anti-Scl 70) also reagent, was under outpatient follow-up at the service rheumatology sector. The patient had no other comorbidities or relevant medical history.

In the occasion, he sought medical care and had progressive dyspnea during minor efforts, edema on lower limbs and dry cough. This clinical condition began five months earlier.

Physical exam showed good general state, with 92bpm heart rate and 80/60mmHg blood pressure, 60<sup>o</sup> jugular turgidity and peripheral perfusion unchanged.

When examining the lungs, vesicular breath sounds was significantly reduced, with velcro-type rales in both bases. Precordium and abdomen exams showed no changes.

There was a severe skin tightening on hands and forearms, with limited movements, contracture flexion and tendon retraction, giving the appearance of "claw hands", and digital ulcers.

Lower limbs showed the same skin severity level, also with movements limitation and edema + +/+4 on the distal 2/3. On the skin we noticed several pigmentary changes on hands, forearms, chest and abdomen. However, skin biopsy was not performed.

Chest computed tomography showed diffuse interstitial pulmonary fibrosis, characteristic of usual interstitial pneumonia with subpleural involvement and regions

### Keywords

Heart Failure; Scleroderma, Systemic; Pulmonary Fibrosis; Pericarditis.

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with "ground glass" appearance, in addition to distortion signs of the pulmonary parenchyma, with reticulate and images that suggest bronchiectasis, specially in lower limbs (Figure 1). On the mediastinal window there was a suggestive image of pericardial thickening, in addition to a small amount of fluid (Figure 2).

In the electrocardiogram there was an atrial fibrillation rhythm, without further changes. Echocardiogram measures are described on Table 1. This exam also identified a mild mitral insufficiency, severe tricuspid insufficiency and signs of severe pulmonary hypertension, being the systolic pressure in pulmonary artery (SPPA) underestimated due to severe tricuspid reflux, with RV – RA gradient of 20mmHg. No changes on pericardium were shown.

After 40 days of hospitalization, he showed a worsening clinical condition and a relevant hemodynamic impairment, which resulted in cardiogenic shock and death.

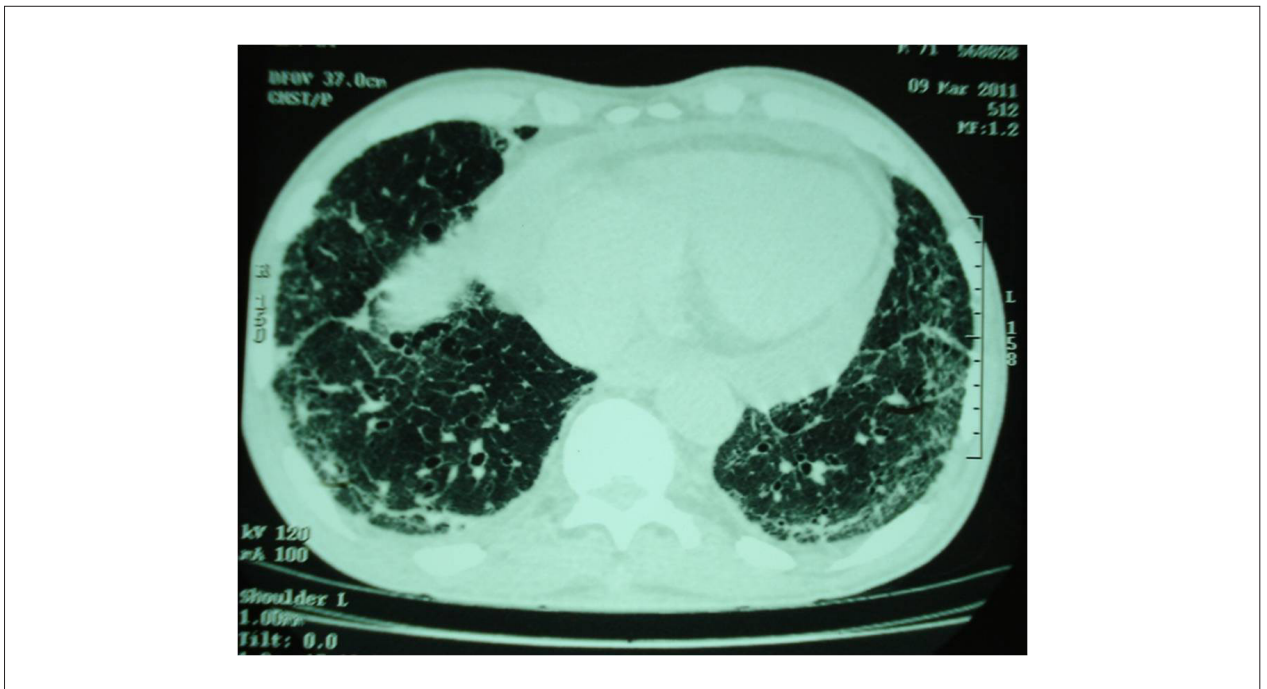
**(Dr. Mariana Bittar Lopes; Academician Caio Bosquiero Zanetti)**

### Clinical aspects

The patient was a healthy male, without comorbidities, who showed a diffuse systemic sclerosis (DSS) condition at the age of 71. It is known that when this autoimmune disease is manifested after the patient is 60 years old, it evolves more rapidly and, therefore, has a worse prognostic<sup>1-3</sup>. With the reported clinical condition, it is hard to elaborate differential diagnosis, because in addition to symptoms and clinical signs on his skin and articulations, immunological evidence were reagent and are positive in 90% of DSS cases, specially anti-centromere antibodies, anti-topoisomerase I and anti-RNA polymerase, which show a specificity of 97-100%<sup>1,4-7</sup>.

Diastolic congestive heart failure (DCHF), in this case, can be a result of the heart impairment caused by DSS, for there are indications of constrictive pericarditis, demonstrated by the pericardial thickening seen in chest computed tomography and left atrium, seen on echocardiogram. DCHF could also be a consequence of the pulmonary hypertension resulting from either the pneumopathy described or pulmonary endarteritis. Atrial fibrillation can be justified by the myocardial impairment of DSS, as well as by the tricuspid insufficiency resulting from the right chambers impairment caused by the pulmonary hypertension.

In this case, the pulmonary impairment pattern demonstrated by the chest computed tomography is not the most common one in DSS. The most frequent is the non-specific interstitial pneumonia<sup>8-10</sup>. However, we cannot discard that the pulmonary impairment identified is a result of chronic inflammatory changes in pulmonary interstice caused by the disease, which are more active ("ground glass" pattern) and already show



**Figure 1** - Chest CT showing a diffuse interstitial pulmonary fibrosis, with subpleural involvement, honeycombing and bronchiectasis, characteristics of a usual pattern of interstitial pneumonia.



**Figure 2** - Chest CT demonstrating pericardial thickening and a small amount of fluid.

older changes, such as pulmonary fibrosis which, by traction, induce bronchiectasis and subpleural thickenings, classifying the tomographic findings as acute exacerbation of the chronic evolution interstitial pneumonia, common on collagenosis<sup>8,11</sup>.

The patient developed cardiogenic shock due to natural progression of heart disease, which worsened due to chronic hypoxia resulting from lung disease or embolism or thrombosis of pulmonary arteries.

**Table 1 - Measures obtained through echocardiogram, showing a moderate dilation on the left atrium**

Analysis	Measure	Analysis	Measure
Aorta	33.00mm	LV – final systolic diameter	21.00mm
Left atrium	48.00mm	LV – final diastolic volume	87.69mm
Left atrium/aorta	1.45mm	LV – final systolic volume	14.41mm
Right ventricle	30.00mm	Shortening fraction	52.27%
Ventricular septum	10.00mm	Ejection fraction	83.57%
Posterior wall	10.00mm	LV mass	147.24g
IV septum/posterior wall	1.00mm	LV mass index	85.80g/m <sup>2</sup>
LV – diastolic diameter	44.00mm	V/M relation	0.60

Thus, it is possible to suggest the following clinical diagnoses: diffuse systemic sclerosis, diastolic congestive heart failure, chronic atrial fibrillation, constrictive pericarditis secondary to DSS, pulmonary fibrosis secondary to DSS, pulmonary arterial hypertension associated with DSS, bronchiectasis and cardiogenic shock. As clinical hypotheses: diffuse systemic sclerosis, diastolic congestive heart failure, constrictive pericarditis secondary to DSS, pulmonary arterial hypertension secondary to DSS, pulmonary fibrosis secondary to DSS, chronic atrial fibrillation and cardiogenic shock.

(Dr. Maria Aparecida Barone Teixeira)

### Necropsy

There was a relevant skin impairment described by the physical examination, histologically revealed in several skin fragments examined, such as a significant increase of compact collagen in dermis, thinning of epidermis, loss of interpapillary crystals, hyperpigmentation of melanocytes, adnexal atrophy, hyaline thickening of dermal arteriolar walls and perivascular and perianexial inflammatory process.

There was a thickening of pericardial sac with high adherence between the parietal and visceral pericardium, and only 17mL of bloody pericardial fluid. The microscopic study revealed a severe fibrinous chronic pericarditis (Figure 4). Right heart chambers and pulmonary trunk were dilated, in addition to the dilation of tricuspid ring. Cross-section of the heart showed small fibrosis foci distributed over the left ventricle, specially in subendocardial regions, histologically identified as thick fibrous ridges, and high increase of interstitial collagen, constantly changing the structure of muscle fibers (Figure 5 and 6). Moreover, throughout the myocardium were identified moderate/severe hyperplastic arteriosclerosis and areas of degeneration and band necrosis of myocytes (Figure 5), probably due to ischemic component associated with arteriolar disease, common in diffuse systemic sclerosis.

Lungs had increased consistency, moderate pleural thickening and were wine-colored, which suggested venous congestion. When cutting, there was a severe fibrosis with thickening of intralobular septa and increased airways, often converging and forming cystic structures, leading to

honeycombing. Histologically, pulmonary parenchyma showed high thickening of alveolar septa due to conjunctive tissue, destruction of walls due to increased airways, bronchiectasis and, predominantly, bronchioloectasia, in addition to severe hyperplastic arteriosclerosis in all fragments, changes that characterize the pulmonary involvement of the disease.

Other organs did not show significant changes.

Anatomopathological diagnosis: chronic fibrosing pericarditis, myocardial fibrosis, myocardial arteriosclerosis, chronic passive pulmonary congestion, intralobular pulmonary fibrosis, bronchiectasis and bronchioloectasia, and pulmonary arteriosclerosis.

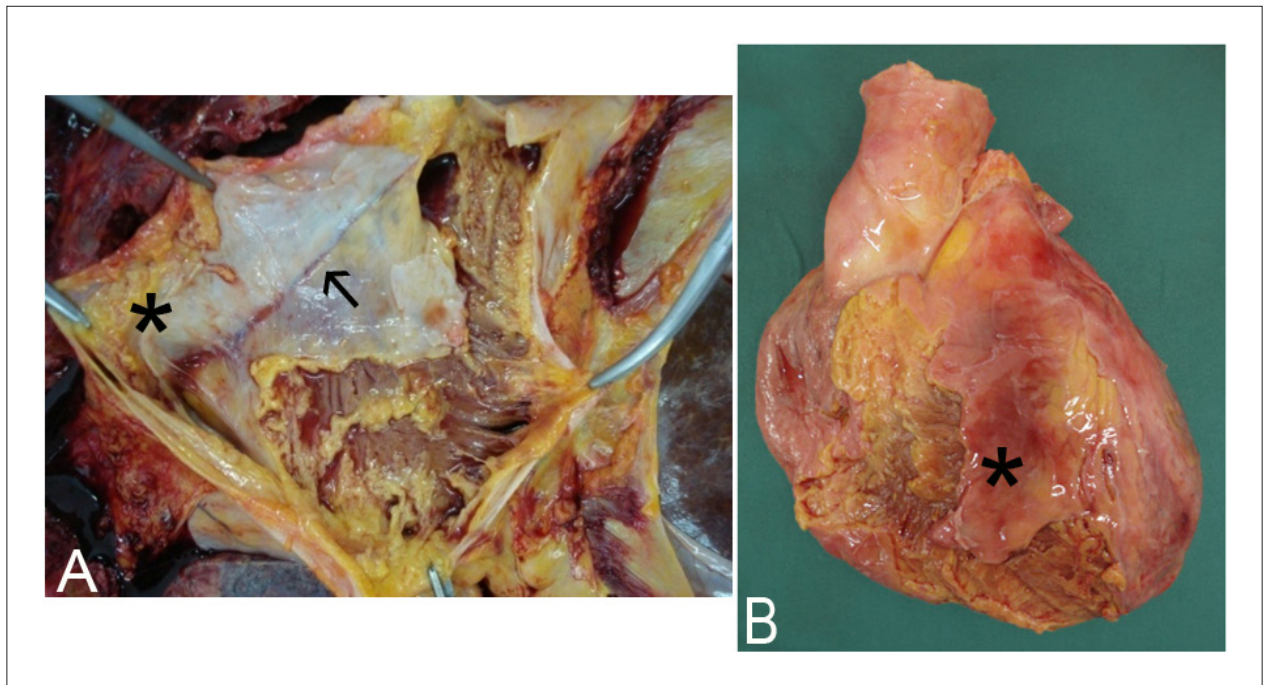
(Dr. Pompeu Ribeiro de Campos)

### Clinical comment

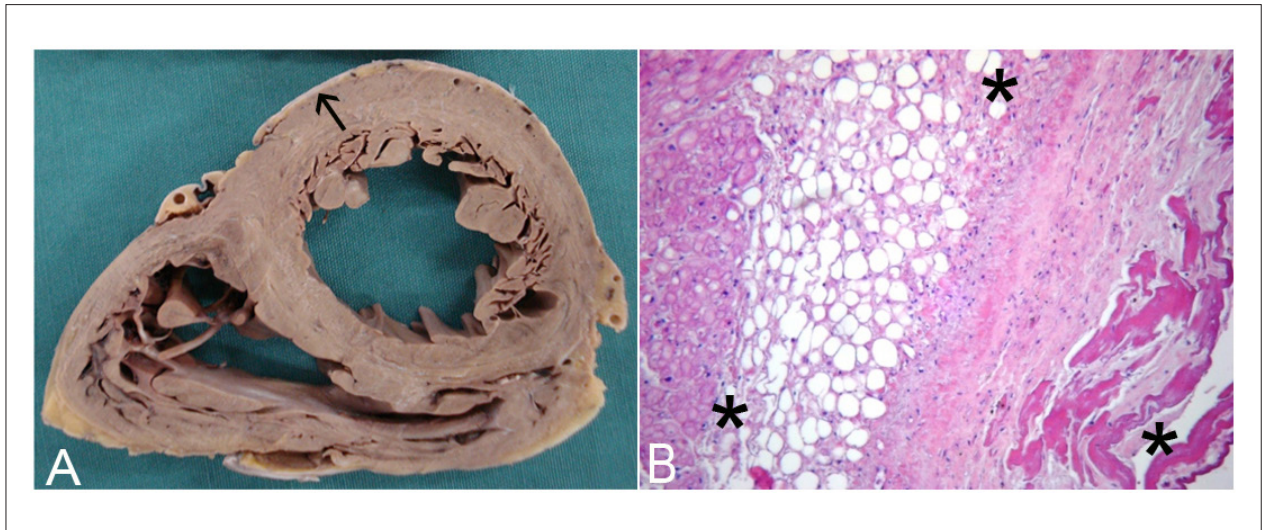
Firstly described by Carlos Curzio (Naples, 1753), Scleroderma, currently known by Systemic Sclerosis (SS), is an chronic idiopathic inflammatory disease, characterized primarily by proliferative endarteritis, and increased conjunctive tissue on skin and internal organs, specially in lungs, gastrointestinal tract, heart, and kidneys. With prevalence that varies from 30 – 290 cases per million inhabitants, usually begins between the 3rd and 6th decade of life, and is more common in females with a proportion ranging from 3 – 8 women for each man<sup>2</sup>.

It can manifest itself in a limited way, basically restricted to skin in distal, or diffuse, portions, affecting the skin not only distally, but also the face, trunk, and abdomen, in addition to rapid progress and severe visceral impairment.

Its pathogen is not completely clear, however, it is believed that there are interactions between genetic factors and immunological changes involved in the development of the disease. In principle, there is an increased activity of genetically pre-determined T lymphocytes, which through inflammatory factors, such as interleukins 3 and 4, promote the mast cells degranulation. These mast cells cause the increased significance of the growth factors of fibroblasts and endothelial cells. Thus, it is an abnormal endothelial proliferation, specially in microcirculation, changes in vasoreactivity, coagulation processes, and modulation of the



**Figure 3 -** (A) Macroscopic view showing severe thickening of pericardial sac (asterisk) and adherence between parietal and visceral pericardium (arrow); (B) Severe thickening of visceral pericardium (asterisk).



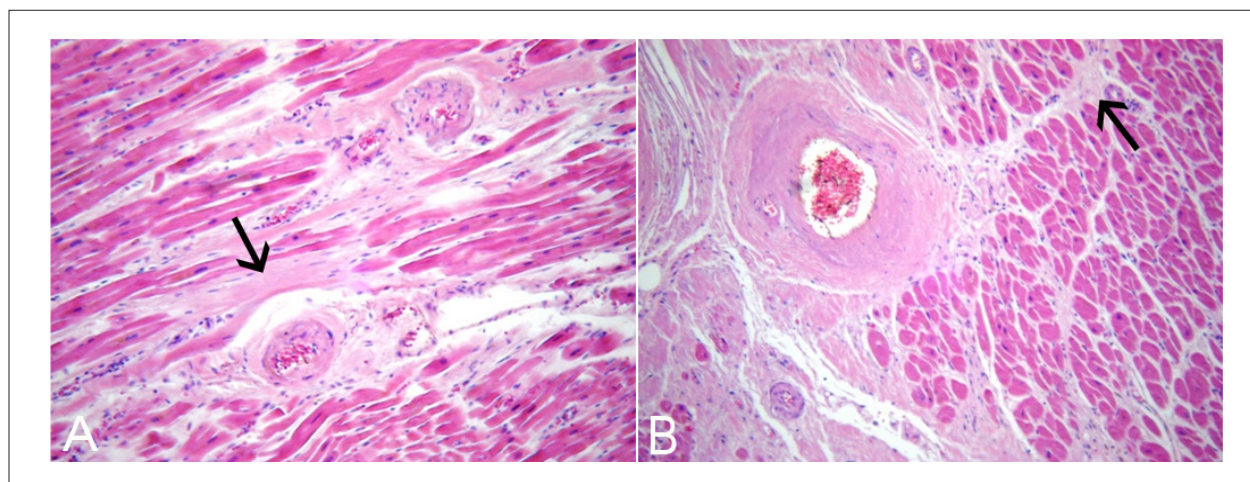
**Figure 4 -** (A) Cross-section showing pericardial thickening (arrow); (B) Severe fibrinous chronic epicarditis (asterisks), eosin haematoxylin (EH) – original magnification 100x.

growth of neighboring cells, such as smooth muscle cells and fibroblasts, in addition to the large increase of secretion of collagen types I, III, and VI, primarily by the action of Transforming Growth Factor Beta (TGF-Beta), resulting in high process of fibrosis<sup>2</sup>.

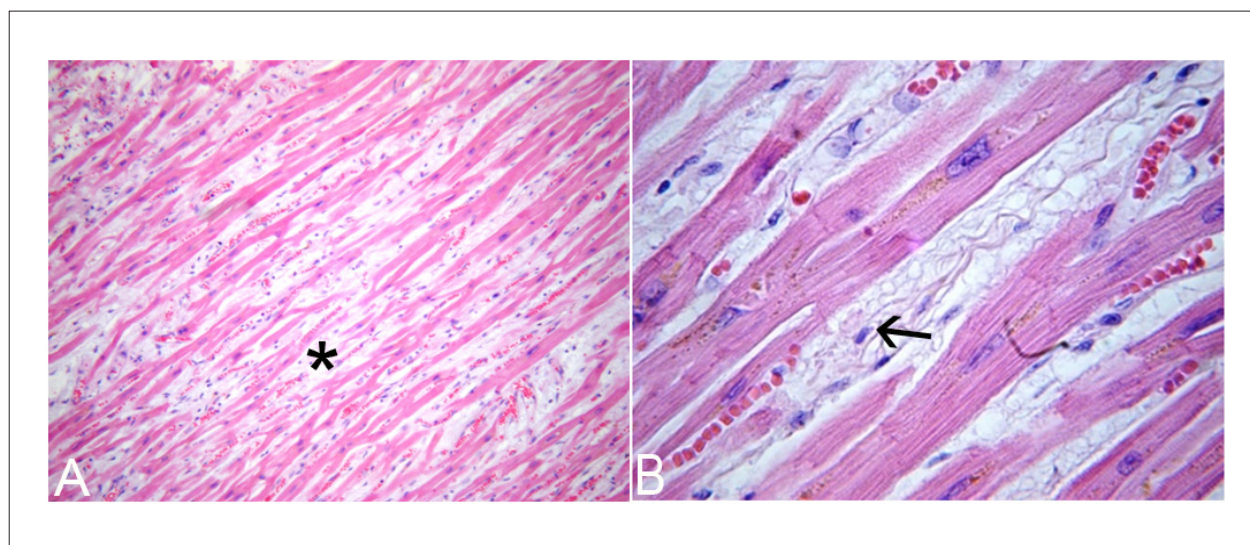
As for the heart, the heart impairment in diffuse disease is found in 32% of patients<sup>3,12</sup>, and may involve the pericardium, coronary arteries, conduction system, and

myocardium, which is the most affected region<sup>13</sup>. Based on clinical criteria, the prevalence of myocardopathy varies between 20 – 25% of patients with DSS<sup>13-15</sup>, a number that can reach up to 70% of cases in necropsy studies<sup>16</sup>. Anatomically, the most common findings are band cell necrosis and foci of myocardial fibrosis, equally distributed between the right and left ventricles and mainly involving subendocardial regions. In functional terms, systolic left ventricle failure is most often subclinical, reducing

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**Figure 5** - Cut of subendocardial region with increased interstitial collagen and thick fibrous ridge (arrows), changing the muscle fibers structure. Also note the moderate/severe hyperplastic arteriosclerosis and degeneration areas of myocytes due to arteriolar disease, eosin haematoxylin (EH) – original magnification 100x (A and B).



**Figure 6** - Increased conjunctive tissue between heart muscle fibers (asterisk) with presence of fibroblasts (arrow), eosin haematoxylin (EH) – original magnification 100x (A) and 400x (B).

the ejection fraction by echocardiogram in only 11% of patients<sup>13,19,20</sup>. Frank congestive heart failure occurs in cases of advanced disease, and right ventricular failure is most often a result of pulmonary hypertension, both are factors of worse prognosis.

Pericardial changes are found in 33 – 72% of necropsies<sup>16,21</sup> and consist of pericardial fibrosis, fibrinous pericarditis, pericardial adhesions and stroke. However, clinical manifestations of the pericardial disease occur in only 7 – 20% of patients. Small accumulation of pericardial fluid and chronic strokes are present in 35% of cases by echocardiogram<sup>16,22</sup>, generally asymptomatic, are related to pulmonary hypertension<sup>13,23,24</sup> and, also, a poor prognosis. We must also remember the concept of *concretio cordis*, a

rare heart manifestation of DSS, related to severe constrictive pericarditis resulting from high fibrotic process, severe pericardial thickening and ectopic calcifications<sup>25,26</sup>.

Changes in epicardial coronary arteries are not common and the coronary atherosclerosis is not related to DSS<sup>13-15</sup>. However, 40 – 70% of asymptomatic patients have perfusion abnormalities at rest, identified by scintigraphy with Thallium-201, and 38% have flow alterations induced by stress<sup>15, 16</sup>. Studies show that such events are due to intimal proliferation, mural fibrosis, and endothelial proliferation of intramural arteries and microcirculation, characterizing hyperplastic arteriosclerosis, common in DSS<sup>16</sup>. Overall, evidence suggest abnormalities in vasoreactivity and transitory constrictions in small arteries and arterioles, contributing to ischemic events of the myocardium.

In addition to the aforementioned, are also factors of worse prognosis: rapid progression of skin sclerosis, linked to early cardiac involvement in 41% of cases<sup>12</sup>, cardiac involvement at diagnosis, associated with a mean survival of 32 months<sup>16</sup>, and clinical manifestations resulting from heart impairment, determining a death rate of up to 70% in five years<sup>13</sup>. Pulmonary involvement, wither pulmonary hypertension or restrictive pulmonary disease, defines a mean survival of 78 months after the diagnosis<sup>16</sup>.

(Dr. Rubens Bonfiglioli; Dr. André Marun Lyrio)

## Comment

After the necroscopic study, we can confirm the usual interstitial pneumonitis pattern, shown by simple radiography and chest CT, DSS typical pulmonary alteration in advanced stage. We also demonstrated the pericardial alterations that led to constrictive pericarditis, which justifies part of the heart failure condition and confirms the CT cardiac findings, despite of not having been identified by echocardiogram, a method introduced in the literature as the test selected to identify pericardial effusions, offering high sensitivity and specificity<sup>27</sup>.

DCHF also had the interstitial fibrosis as anatomic substrate replacing myocardial fibers. In this case, the increased interstitial collagen can be attributed to both

intramyocardial hyperplastic arteriolosclerosis, leading to relative muscle ischemia, or the disease pathogenesis, which may have activated growth factors of fibroblasts of the cardiac interstitium.

Finally, pulmonary hypertension can be justified, in this case, by the heart impairment resulting from DSS, but also, and primarily, by the severe hyperplastic arteriopathy, attributed to diffuse interstitial pulmonary fibrosis, justifying the dilation of right chambers and pulmonary arteries, and tricuspid reflux found on echocardiogram, and which also contributed to the patient's heart failure condition.

In our case, unlike the epidemiological data, the patient was male and had older age at the disease onset. It should also be noteworthy the rapid progression between the first signs of the disease and death, which occurred after 8 – 9 months. Such fact can be explained by the presence of several worse prognosis factors described throughout the medical history: (1) rapid progression of skin disease, (2) cardiac involvement at diagnosis, (3) presence of clinically evident pericarditis and pericardial effusion, and (4) advanced pulmonary impairment. The necropsy findings coincide with the anatomopathological descriptions in the literature, and classify the patient as having rapidly progressive DSS in advanced stage.

(Dr. Maria Aparecida Barone Teixeira; Academician Caio Bosquero Zanetti)

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