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Death occurred due to undiagnosed systemic amyloidosis: a case report

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Abstract

Amyloidosis is a disorder related to errors in protein folding. We present a clinical case of systemic amyloidosis manifesting as hypotension, tachycardia, pain, weight loss, asthenia, anorexia, dysphagia, and mood deflection in a 49-year-old-year-old woman with a previous clinical history of articular and muscular pain, correlated to suspected seronegative arthritis. The blood test revealed kidney insufficiency, an electrocardiogram identified low voltages of the peripheral leads and T waves anomalies. A serum protein electrophoresis revealed the presence of high levels of monoclonal kappa free chains. The woman started to have a sense of suffocation, and after one week she was found dead in her bed. After the autopsy, the results of Congo red staining of the myocardium were characteristic of amyloid. According to the autoptic and the histological examination, death occurred due to acute cardiac and respiratory arrest secondary to amyloid cardiomyopathy in a patient with undiagnosed systemic amyloidosis. ***Clin Ter 2022; 173 (6):516-519 doi: 10.7417/CT.2022.2473***

Key words: *amyloidosis, case report, autopsy, heart failure, Congo Red staining, immunohistochemical staining*

Introduction

Amyloidosis refers to a group of disorders related to errors in protein folding. Amyloid deposits appear as proteinaceous amorphous fibrils (β-plated sheet) (1,2) in parenchymal organs. Systemic amyloidosis can be hereditary (ATTR) or acquired (AL). Hereditary amyloidosis is most commonly referred to as missense mutation of precursors proteins, mainly transthyretin (ATTR) (3), while acquired amyloidosis is most commonly referred to as light chain amyloidosis, generally related to Monoclonal Gammopathy of Undetermined Significance (MGUS), and, more rarely, to myeloma. The protein accumulation can cause a systemic disorder, with kidney insufficiency, dyspnea due to amyloid deposits into the upper airways, and cardiac amyloidosis, which is generally related to a poor prognosis (4,5).

As there are no current therapies to heal amyloidosis, early diagnosis is mandatory to avoid potentially severe consequences, which are more common in cardiac amyloidosis.

The goal of cardiac amyloidosis treatment is to prevent heart impairment and to give supportive therapy according to the clinic.

Case description

Our case is related to a 49-year-old woman with a previous clinical history of articular and muscular pain, correlated to suspected seronegative arthritis, successfully treated with corticosteroid therapy. The woman complained also about dysphagia and anorexia related to suspect gastroesophageal reflux.

The woman was admitted to the Emergency Department complaining about the fear of sudden death. Her vital parameters revealed hypotension (arterial pressure 93/70 mmHg), tachycardia (107 beat/min), and O2Sat 98%. She also referred to pain, weight loss, asthenia, anorexia, dysphagia, and mood deflection.

The blood test revealed kidney insufficiency (creatinine 1.9 mg/dl, VFG 26.4 ml/min/1.73 mq), at first considered secondary to dehydration. A psychiatric evaluation diagnosed a possible personality disorder with depressive symptoms, hypochondria, and a sense of impending doom. For these reasons, the patient was admitted to the Psychiatric Ward.

Despite the rehydration therapy, during the hospital stay the patient had a constantly low arterial pressure (60/80 mmHg), dysphagia, increased creatinine (2.12 mg/dL), and serum calcium levels (12.6 mg/dL), and she developed dyspnea. A nephrological evaluation suggested monitoring daily diuresis and proteinuria. An abdominal ultrasound was suggestive of chronic nephropathy, in disagreement with the hypothesis of new-onset kidney disease due to dehydration. An electrocardiogram was consistent with low voltages of the peripheral leads, and T waves anomalies. A serum protein electrophoresis revealed the presence of high levels of monoclonal kappa free chains. The patient started to complain

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about a sense of suffocation, associated with secretions of the upper respiratory ways. After one week of clinical staying, the patient was found dead in her bed.

An autopsy was required to ascertain the cause of death.

The heart (240g) had a macroscopic aspect consistent with hypertrophic cardiomyopathy; the lungs (right 550g, left 570g) showed massive edema; the kidneys had cortical marbling.

Histological evaluation revealed interstitial (Fig.1b) and perivascular (Fig.1c) deposits of amyloid under the polarized light microscope by Congo Red histochemical staining (Fig.1b, c, d). Single myocytes were surrounded by the fine amyloid deposition (Fig.1d). The amyloid deposits were shown to be constituted by K light chains of Immunoglobulins by immunohistochemical staining, with an evident strong interstitial (Fig.2a) and perivascular (Fig.2c) positivity for K light chains of Immunoglobulins versus negative immunostaining for lambda light chains of Immunoglobulins in both myocardial interstitium (Fig.2b) and perivascular (Fig.2d) spaces.

Lung histology revealed massive edema, and sporadic interstitial deposits with giant cells pattern. Kidney histology was consistent with amyloid deposits with giant cells pattern, and focal glomerulosclerosis. The histology of the upper airways (trachea, larynx, esophagus) revealed fibrosis and deposits with giant cells pattern.

According to the autoptic and the histological examination, death occurred due to acute cardiac and respiratory arrest secondary to amyloid cardiomyopathy in a patient with undiagnosed systemic amyloidosis.

Discussion

Cardiac amyloidosis is a potentially lethal condition, frequently associated with unspecific symptoms. The diagnosis is based on a three-step pattern: 1) suspicion; 2) diagnosis; 3) characterization of amyloid type (6). The clinical examination can suggest the suspicion of amyloidosis, which is based on: kidney function impairment and/or proteinuria; swollen ankle; dyspnea on exertion; fainting; heart failure; tingling; pain and sensitive alteration in hands and feet; intestinal symptoms, such as diarrhea or constipation (7).

Diagnosis is based on serological tests, revealing serum natriuretic peptides and troponin as biomarkers of heart failure. cTnT elevation is a poor prognosis factor (8,9). Electrophoresis to detect serum and urine free light chain is highly sensitive for monoclonal gammopathies. Electrocardiogram can reveal the most common abnormalities of amyloidosis, represented by low QRS voltage (<1 mV in all precordial, or < 0.5 mV in all limb leads), and Q waves in precordial or inferior leads with a pseudo-infarct pattern. Conduction alterations due to cardiac amyloid deposits are also frequent.

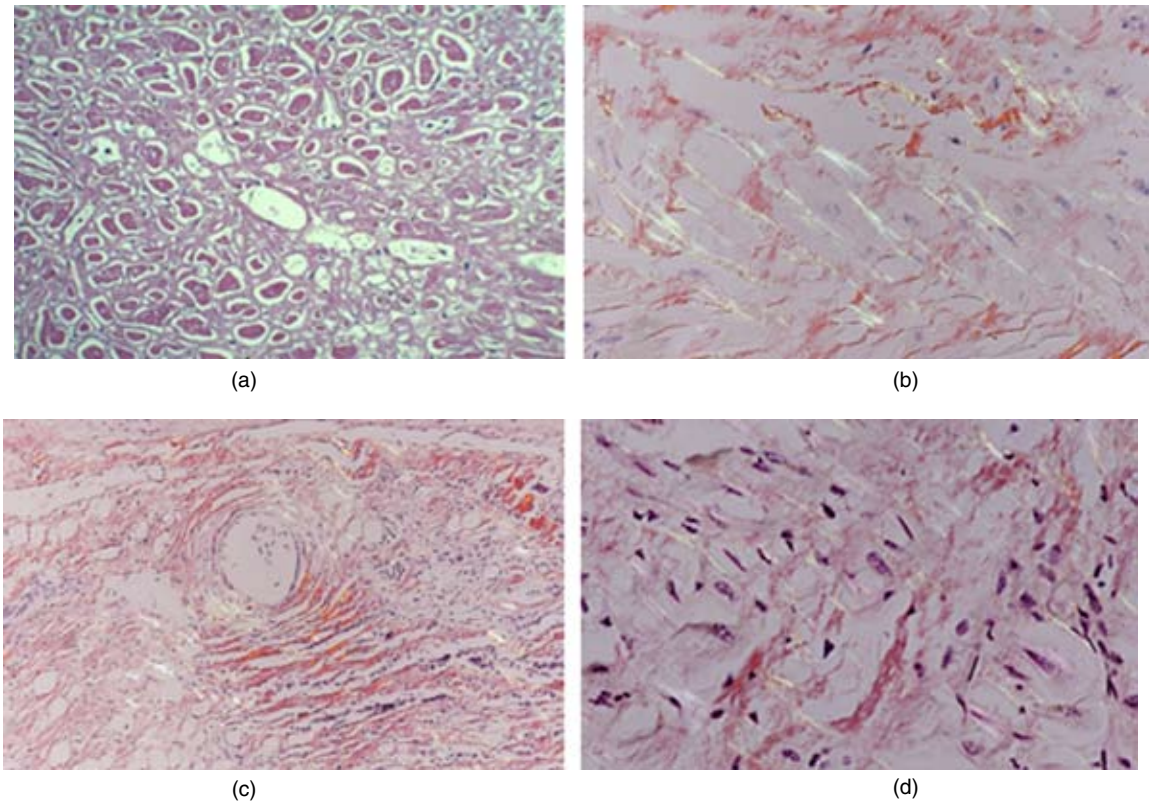

Fig.1 Eosin-Haematoxylin (a) showed proteinaceous amorphous deposits. Congo Red magnification 40x: interstitial (b), perivascular (c), and perimyocyte (d) amyloid appears as apple green deposits under the polarized light microscope

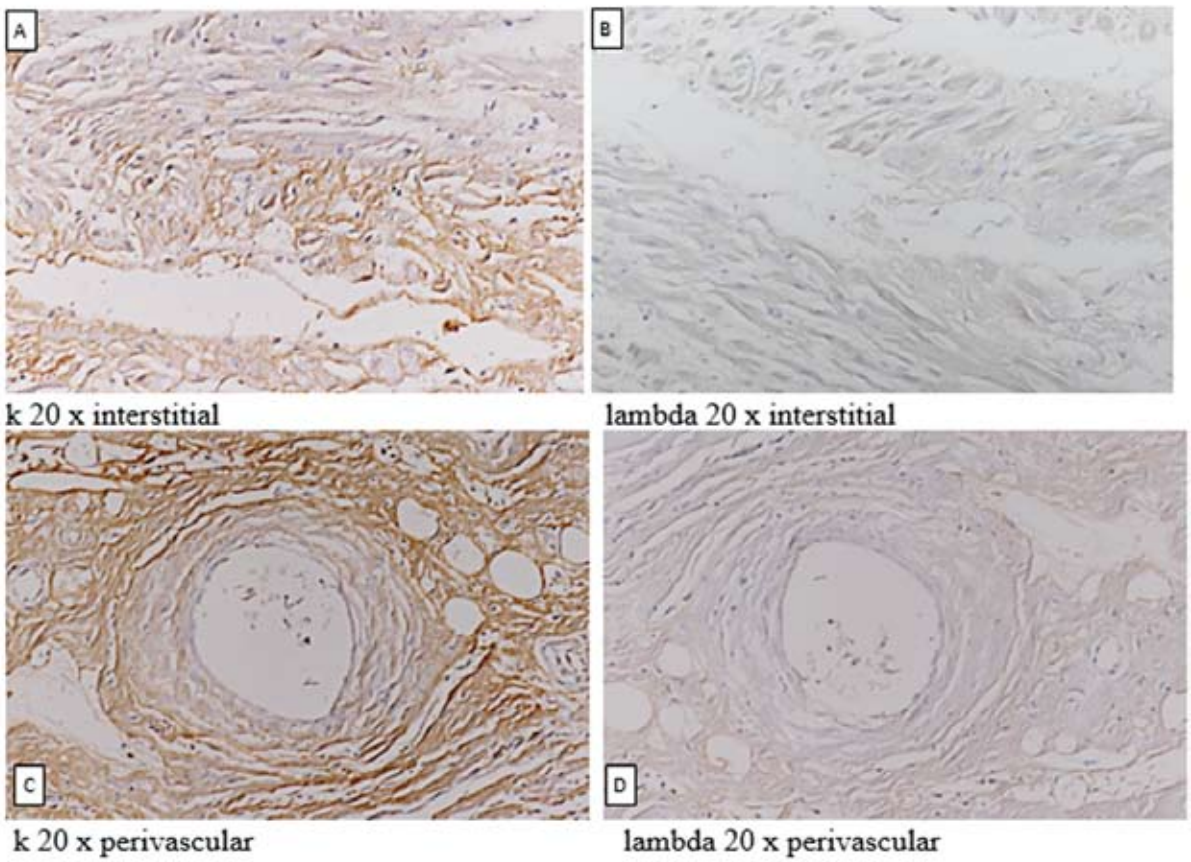

Fig.2 Immunohistochemical staining (magnification 20x) showed strong interstitial (a) and perivascular (c) positivity for K light chains of Immunoglobulins versus negative immunostaining for lambda light chains of Immunoglobulins in both myocardial interstitium (b) and perivascular (d) spaces

Echocardiography is mandatory to demonstrate biventricular concentric wall thickness and reduced endocavitary size, although a differential diagnosis with other hypertrophic and restrictive heart diseases is necessary. CMR can reveal late gadolinium enhancement (LGE), indicating the expansion of the extracellular volume caused by the amyloid deposits in the myocardial tissues.

The diagnosis is confirmed by histologic analysis of fatty tissue biopsy or aspiration, generally sampled from the periumbilical tissues. Other organs that can be examined are the heart, kidney, and liver, according to clinical presentation. Amyloid appears as reddish deposits with Congo red stain at light microscopy, exhibiting green birefringence under polarized microscopy.

The third diagnostic step, which includes amyloid characterization is achieved by histological techniques, which have a fundamental role in Forensic Pathology (10-12). Whole blood electrophoresis is used to distinguish between AL and non-AL-typing amyloid. Electron microscopy is used as well for the diagnosis of amyloid fibrils. The most reliable diagnostic method is mass spectrometry proteomic analysis, which can detect the biochemical characteristics of the protein deposits, with high sensitivity and specificity (13,14).

The chemical differences of the protein deposit make the clinical presentation heterogeneous, representing a challenge (3), and increasing the risk of diagnostic delays (15).

Conclusion

Cardiac amyloidosis is a manifestation of a systemic disease related to amyloid deposition in several tissues. Up to 50% of patients with cardiac amyloidosis die suddenly. Clinical manifestations of amyloidosis are unspecific, making diagnosis delays a real possibility.

Including amyloidosis in the differential diagnosis of patients admitted with systemic unspecific symptoms and instrumental cardiac alterations, is mandatory to prevent a potentially lethal condition.

Learning objectives

Symptoms of systemic amyloidosis are unspecific.

Up to 50% of patients with cardiac amyloidosis die suddenly.

Amyloidosis diagnosis is based on suspicion, diagnosis, and typing.

Low QRS voltage, Q waves in precordial or inferior leads, and cardiac hypertrophy of unknown origin can be the expression of cardiac amyloidosis.

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