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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Cardiac amyloidosis and *Mycobacterium tuberculosis* infection

Amyloidosis is an uncommon condition characterized by extracellular deposition of insoluble protein fibrils, causing structural and functional disorders and consequently modification of the organic structure of organs; cardiac involvement is frequent in amyloidosis. We describe the case of a 36-year-old man with cardiac amyloidosis associated with *Mycobacterium tuberculosis* infection, and who died shortly after the diagnosis was confirmed. The clinical characteristics of the condition and diagnostic investigation are described, and comment is made on the current limitations related to specific management options in clinical practice. The objective of the present report is to enhance the awareness of non-specialists about the diagnosis of this uncommon condition in the primary health care setting.

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Καρδιακή αμυλοείδωση και λοίμωξη από *Mycobacterium tuberculosis*

Περίληψη στο τέλος του άρθρου

Key words

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Amyloidosis is a condition characterized by extracellular deposition of low molecular weight amyloid fibrils, which affect the body locally or systemically, and its manifestations depend on the extent of the deposits and the nature of the tissues involved.[1–12] In western countries the incidence of primary amyloidosis (AL) is 1.0 per 100,000 person-years, and secondary (AA) amyloidosis is associated with chronic inflammatory and microbial diseases, and malignancies.[1,10] Utilizing polarized light microscopy on the tissue samples stained by Congo red, the amyloid deposits display a characteristic apple-green birefringence stain.[1–3,7,12] According to the protein component of the fibrils, amyloidosis is classified into: primary or light chain (AL), with deposition of immunoglobulin light chain fragments, secondary (AA) with deposition of serum amyloid A protein, and transthyretin amyloidosis (ATTR), which may be familial or mutant (ATTRm) or wild type (ATTRwt). In addition, it can be categorized as organ-specific amyloidosis, dialysis-related amyloidosis and hereditary amyloidosis.[1–3,5,7,12] Over 95% of cases of cardiac involvement in amyloidosis develop in patients with ATTR or AL types, and it manifests with the characteristics of infiltrative cardiomyopathy.[2,3,9,12] As the clinical manifestations are nonspecific, the suspicion about, and diagnosis of this entity constitute a challenge. In the case of AL, multiple organs are frequently affected, ATTRm involves the heart and the peripheral or autonomic nervous system, while ATTRwt more commonly develops primarily in the heart.[1–3,7,9,12]

We report the case of a patient who presented cardiac amyloidosis secondary to *Mycobacterium tuberculosis* infection, who also had pulmonary and renal complications.

CASE PRESENTATION

A 36-year-old male was admitted to the emergency department with diastolic heart failure (oliguria, dyspnea on exertion, and lower limb edema for two months), in addition to weight loss over six months. He reported no comorbidities or ongoing medication. On physical examination, he showed dyspnea at rest, edema of the lower limbs and scrotum, and signs of ascites. Imaging studies confirmed the presence of ascites and pleural and pericardial effusions. The echocardiogram (fig. 1) revealed accentuated concentric hypertrophy of the left ventricle (LV) with a granular aspect suggestive of deposit disease, and signs of increased filling pressures, moderate increase of the right atrium, hypertrophy of the right ventricle, and discrete pericardial effusion.

On the 18th day, he developed arterial hypotension and signs of cardiac tamponade and underwent chest drainage and left pleurodesis, but with no improvement. Histopathological studies of pericardial specimens revealed amyloid deposits stained with Congo red dye, and further evaluation by polarized light microscopy showed a green birefringence (fig. 2). The pleural fluid analysis showed red cells: 5,100, leukocytes: 170 (neutrophils: 37%, lymphocytes: 58%, monocytes: 4%, basophils: 1%, and eosinophils: 0); glucose: 100 mg/dL, globulins: 1.2 g/dL, albumin: 0.3 g/dL, DHL:

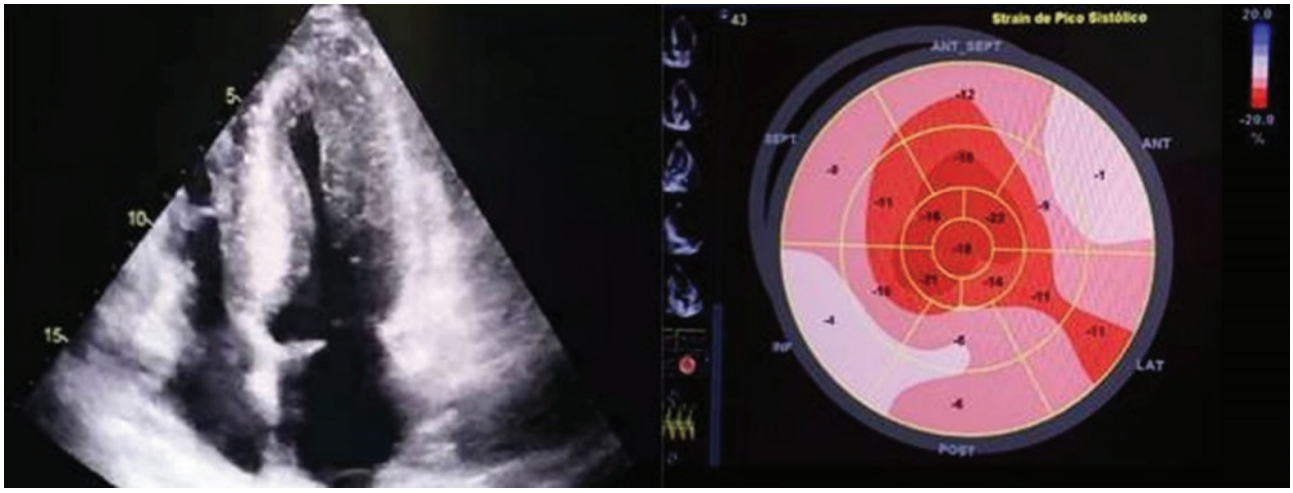

Figure 1. Cardiac amyloidosis in a 36-year-old male: Echocardiography showing accentuated concentric hypertrophy of the left ventricle with an appearance suggestive of a deposit disease and signs of increased filling pressure, moderate increase of the right atrium and hypertrophy of the right ventricle.

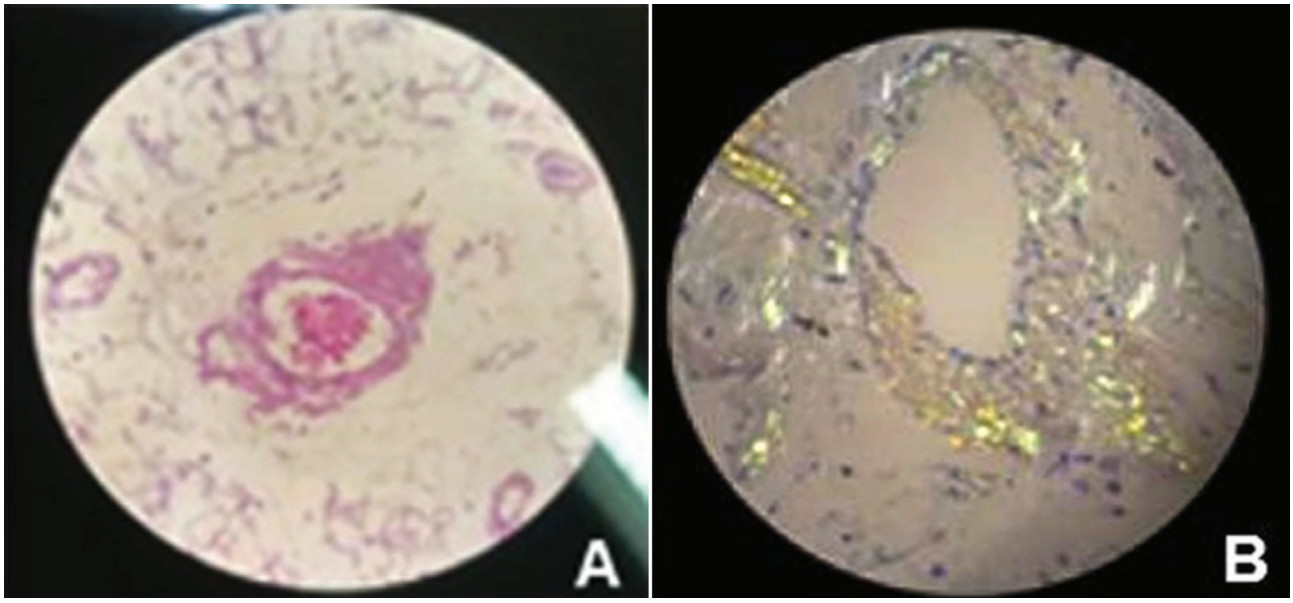

Figure 2. Cardiac amyloidosis in a 36-year-old male: Photomicrographs with Congo red staining of a pericardial biopsy sample. (A) The myocardial amyloid deposits appear reddish around the vessels, and (B) present a green birefringence utilizing the polarized light microscope.

278 IU/dL, and amylase: 15 IU/dL. Acid-fast bacillus (AFB) screening and culture for mycobacteria were negative, the GeneXpert MTB/RIF was positive, with an inconclusive rifampicin-resistant test. Following administration of treatment with rifapentine, isoniazid, pyrazinamide, and ethambutol (the RIPE regimen), he developed pre-renal acute renal failure. Septic shock occurred on the 30th day, which was controlled by meropenem and vancomycin in addition to vasoactive drugs. On the 53rd day, cardiorespiratory arrest occurred, which was refractory to resuscitation and caused his death.

DISCUSSION

Cardiac amyloidosis is an infrequent condition that can evolve unsuspected because there is no classic clinical presentation. It should be considered when the patient presents a restrictive pattern of heart failure, especially in those over 50 years of age, but not excluding individuals in younger age groups.[1,3,7,9,12] It can manifest as an edemagenic syndrome, with ascites, lower limb edema and dyspnea. Syncope may occur with the evolution of the condition reaching symptoms of low cardiac output, progressive hypotension, and cardiogenic shock.[1–3,6,7,9,12] Renal involvement is diagnosed by biopsy and commonly develops in patients with AL amyloidosis.[1,2,9]

Non-invasive resources to evaluate the presence of cardiac amyloidosis include electrocardiogram (ECG), echocardiogram, cardiac biomarkers, cardiac scintigraphy, and magnetic resonance imaging (MRI),[1–4,6–9,11,12] which can show amyloid deposits in cardiac tissues by delayed enhancement technique, even in patients with normal function.[6,9] MRI also contributes to the characterization of the subtypes, for example, the predominant subendocardial amyloid deposits in AL and the transmural deposits in ATTR.[3,4,6,8,9,11] On echocardiography, the amyloid deposits appear more frequently in the middle and basal portions of the ventricles, sparing the apex.[6,9] The wall thickness of the LV in cardiac amyloidosis may be almost double the normal range in the middle and basal areas, while at the apical region the increased wall thickness is only 26%.[8] Initially, the images more often reveal impaired myocardial relaxation, with preserved systolic function, progressing to systolic failure following further depositions.[6]

Suspicion of cardiac amyloidosis should arise in patients with renal and heart failure of unknown cause, and low voltage on the ECG despite the presence of ventricular hypertrophy (due to amyloid deposits), intractable chronic heart failure of unknown cause in people older than 50 years, and elderly patients with coronary disease and rapid deterioration of ventricular function without acute myocardial infarction.[2,7] The main differential diagnostic hypotheses include cardiomyopathy (hypertrophic and ischemic), hypertensive heart disease, and Fabry and glycogen deposit diseases.[3,6,8,9,12]

Treatment of low-risk patients with amyloidosis includes stem cell transplantation, and administration of melphalan, cyclophosphamide, bortezomib, and dexamethasone in cases of bone marrow infiltration with more than 10% plasma cells, or when transplant is refused.[1,12] Cardiac involvement is critical for the prognosis and treatment of systemic amyloidosis; in addition to treatment for heart failure, and installation of a pacemaker or automated defibrillator, options for cardiac amyloidosis are chemotherapy, tafamidis, diflunisal, and heart transplantation.[9] Of note, there are major concerns about the place of heart transplantation, due to scarce experience and the evidence of amyloid deposits affecting the transplanted organ.[2,7]

The singularity of the present case study is the involvement of the heart by amyloidosis in association with an unsuspected extrapulmonary tuberculosis infection. The definitive diagnosis was confirmed by myocardial biopsy, with sensitivity around 100%, when samples stained with Congo red dye examined under polarized light showed an apple-green birefringence.[1–3,7,12] Additional comments on the role played by *M. tuberculosis* infection in the development of amyloidosis, a phenomenon studied since the early 1900s, are related to increased protease cleavage of serum amyloid A causing deposits as amyloid fibrils.[5] Membrane-bound endopeptidase is one of main factors of macrophage recruitment in tuberculous lesions, and serum amyloid A shows a high affinity for the macrophages.[5] A recent concern in this setting is the association of amyloidosis with abnormal protein homeostasis in patients presenting severe COVID-19 inflammatory manifestations.[10] When autophagosomes and proteasomes do not eliminate the altered serum proteins, the fragments can start amyloid genesis, with subsequent development of amyloidosis; follow-up of inflammatory markers and investigation for amyloidosis must be made in severe cases.[10]

CONCLUSIONS

Cardiac amyloidosis is an uncommon cause of restrictive cardiomyopathy that may be underdiagnosed or diagnosed late, and which should be suspected in the case of diastolic heart failure without any other definite cause that could justify this clinical condition. The authors strongly believe that case studies of uncommon conditions can contribute to enhancement of the suspicion index of health care workers, and may increase early diagnosis.

ΠΕΡΙΛΗΨΗ

Καρδιακή αμυλοείδωση και λοίμωξη από *Mycobacterium tuberculosis*

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Η αμυλοείδωση είναι μια σπάνια κατάσταση που χαρακτηρίζεται από εξωκυτταρική εναπόθεση αδιάλυτων πρωτεϊνικών ινιδίων, προκαλώντας δομικές και λειτουργικές διαταραχές με συνέπεια τροποποίηση της δομής των οργάνων. Η καρδιακή προσβολή είναι συχνή. Περιγράφεται η περίπτωση ενός άνδρα 36 ετών με καρδιακή αμυλοείδωση που σχετιζόταν με λοίμωξη από *Mycobacterium tuberculosis*, ο οποίος κατάληξε λίγο μετά τη διάγνωση. Σχολιάζονται τα κλινικά χαρακτηριστικά και τα συμπληρωματικά στοιχεία για τη διάγνωση, εκτός από τους τρέχοντες περιορισμούς που σχετίζονται με την κλινική πρακτική. Σκοπός είναι η ενίσχυση της ευαισθητοποίησης των μη ειδικών αναφορικά με τη διάγνωση αυτής της σπάνιας νόσου, ιδιαίτερα στην πρωτοβάθμια φροντίδα υγείας.

Λέξεις ευρετηρίου: Αμυλοείδωση, Διάγνωση, Καρδιά, Παθολογία, Φυματίωση

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