Case Report

Pulmonary Embolism and Light Chain Cardiac Amyloidosis with Progression to Heart Transplant

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Introduction

Cardiac amyloidosis results from the deposition of amyloid fibrils in the heart's extracellular space.[1] This chronic and progressive disease significantly reduces quality of life and carries a high mortality rate if not diagnosed and treated early.[2] Myocardial damage occurs due to direct injury by blood peptides, as well as architectural distortion caused by the extracellular infiltrate, leading primarily to diastolic ventricular dysfunction but also systolic dysfunction, as the disease progresses and cardiac arrhythmias emerge.[3] The most common subtypes include abnormal transthyretin peptides (ATTR) and immunoglobulin light chain (AL), with AL having a worse prognosis and heart transplantation being a potential treatment option.[3] In the United States, the estimated incidence of light chain amyloidosis cardiomyopathy is 1 in 100,000 individuals.[4,5] The primary risk factor for the development of light chain amyloidosis is a personal history of monoclonal gammopathy.[6]

Cardiac manifestations often involve orthostatic hypotension, arrhythmias, ventricular hypertrophy inconsistent with electrically inactive regions on the electrocardiogram, and heart failure with preserved ejection fraction predominantly, though reduced ejection fraction may occur in advanced cases.[3]

The aim of this article is to outline a case initially diagnosed as pulmonary embolism but later identified as multiple myeloma progressing to light chain cardiac amyloidosis, with a rapid clinical deterioration necessitating heart and bone marrow transplantation. Furthermore, it aims to highlight key aspects of diagnostic suspicion and the criteria for heart transplantation.

Case Presentation

A 47-year-old male patient, an amateur street runner without known comorbidities, sought emergency care due to dyspnea and progressive fatigue while running at a slow pace (7 km/h) on a treadmill and climbing stairs at home over the past month. He also mentioned experiencing new epigastric discomfort and noticing increased abdominal volume.

Clinical examination relevant findings included jugular distension, hepatojugular reflux, palpable hepatomegaly 2 inches below the right costal margin, and clear, rhythmic heart sounds with frequent premature beats, as well as palpable ascites. The electrocardiogram (Figure 1A) indicated sinus rhythm, rightward axis deviation of the QRS complex, atrial chamber overload, and an inactive area in the anterior wall. Laboratory tests revealed a D-dimer level of 1376 ng/mL, stage 1 kidney dysfunction, and myocardial injury with a highly sensitive troponin level of 59 ng/ml.

A chest computer angiotomography confirmed a subsegmental pulmonary embolism (Figure 1B and 1C), requiring hospitalization for anticoagulation. The transthoracic echocardiogram revealed biatrial dilation, moderate right ventricular hypertrophy and dilation, and left ventricular hypertrophy, along with moderate diastolic dysfunction and preserved ejection fraction (Figure 1D). The longitudinal strain was reduced (-7.6%), with a myocardial contractility pattern that preserved the apex at the expense of the mid and basal segments (Figure 1E). There was a significant discrepancy between the electrocardiogram and the echocardiogram, and the apical pattern of longitudinal strain suggested myocardial deposition disease, particularly amyloidosis.

Magnetic resonance imaging confirmed diffuse myocardial thickening, predominantly affecting the left ventricle, along with biventricular systolic and diastolic dysfunction and increased biatrial dilation, while also observed alterations in the blood inversion time of both ventricles (Figure 1F). Pyrophosphate marker scintigraphy showed grade 1 cardiac concentration, i.e., lower than bone uptake.

Serum and urine protein electrophoresis did not detect a monoclonal peak, but serum and urine immunofixation demonstrated a monoclonal peak of free lambda light chain IgG. Bence Jones proteins were identified in the urine. Serum levels were 9.74 for free kappa light chain and 407.74 for free lambda light chain, with a kappa/lambda ratio of 0.02. Bone marrow examination indicated the presence of 11.6% of abnormal plasma cells. According to the bone marrow biopsy, there was 10-15% plasma cell infiltration with light lambda chain immunoglobulin restriction.

Adipose tissue biopsy did not indicate evidence of amyloidosis, but endomyocardial biopsy exhibited birefringence under polarized light (positive Congo Red stain). The patient progressed to INTERMACS 3 and was prioritized on the heart transplant waiting list while receiving dobutamine.

Keywords

Immunoglobulin Light-chain Amyloidosis; Restrictive Restrictive Cardiomyopathy; Heart Failure; Heart Transplantation.

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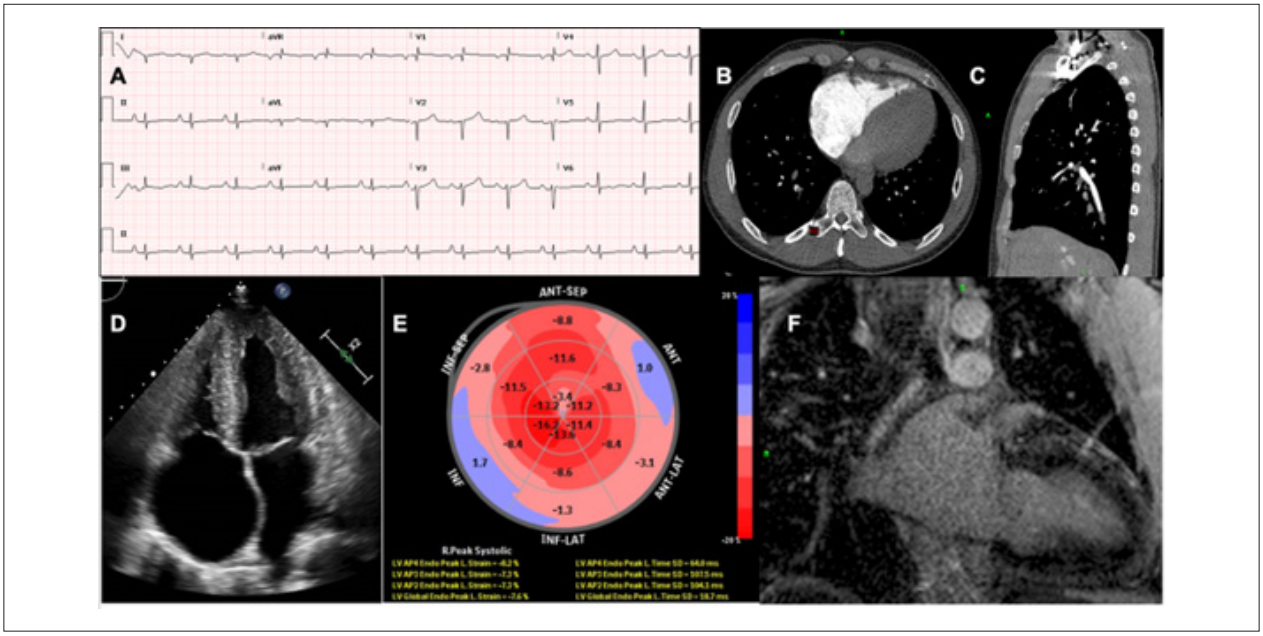

Figure 1 – *A - Electrocardiogram: Sinus rhythm, biatrial overload, S1Q3T3 pattern. Slow progression of R-waves in the precordial leads. B and C - Chest Angiotomography: Acute Pulmonary Embolism in the arterial branches of the basal posterior segment of the lower right lobe. D - Thoracic Echocardiogram: Biatrial enlargement, left ventricular hypertrophy. E - Longitudinal Strain: Apical sparing. F - Cardiac Magnetic Resonance Imaging: T1 Mapping: Alterations in the myocardial blood inversion time sequence, late gadolinium enhancement in the myocardium*

Chemotherapy and immunotherapy with daratumumab, cyclophosphamide, bortezomib and dexamethasone (dara-CyBorD regimen) were initiated. With the treatment directed towards multiple myeloma, normalization of the free lambda light chain and kappa lambda gradient levels was observed.

The patient remained stable on dobutamine for four months while awaiting heart transplantation. Following transplantation, he experienced no postoperative graft rejection and was able to be discharged from his hospitalization. Autologous bone marrow transplantation was performed eight months after heart transplantation, with outpatient follow-up by cardiology and hematology.

Discussion

It is possible that the disease had been silently and progressively developing over the years, leading to a decline in the ability to run long distances. However, given the patient's physical conditioning and decreased running activity during the pandemic lockdown in Brazil, he was able to tolerate well the decline in functional capacity until it reached the point of affecting minimal daily efforts.

From a diagnostic perspective, the patient presented with clinical features of new onset heart failure. Common differential diagnoses include acute coronary syndrome, hypertensive emergency, pulmonary embolism, cardiac arrhythmia, viral myocarditis, and valvular disease. Typically, a personal history of monoclonal gammopathies, other hematologic diseases, a family history of amyloidosis, and cardiovascular, hepatic, or renal disease suggest an increased risk of amyloidosis.[3] In this case, initially, multiple myeloma had not been diagnosed, and there was no family history of the disease.

The electrocardiogram provided valuable information. Signs of rightward deviation of the cardiac axis, associated with an elevated D-dimer, suggested pulmonary embolism as the cause of heart failure. However, a pulmonary embolism with hemodynamic impact is manifested by the presence of the thrombus in the pulmonary artery trunk or the bifurcation of the right and left pulmonary arteries, leading to right ventricular chamber dilation and deviation of the interventricular septum towards the left ventricle, which did not occur in this case.

The discordance between the inactive area and slow progression of the anterolateral wall on the electrocardiogram and the hypertrophy, diastolic dysfunction of the ventricles, biatrial dilation, and characteristic strain indicating dysfunction of the mid and basal segments with preservation of the cardiac apex, forming a "bull's eye," is typical of cardiac amyloidosis. Other electrocardiographic findings that occur in amyloidosis include atrial fibrillation, atrioventricular blocks, left bundle branch block, and low QRS complex voltage. Differential etiological diagnoses for amyloidosis include arterial hypertension with heart hypertrophy, hypertrophic cardiomyopathy, amyloidosis, and Fabry's disease, which were ruled out based on the patient's personal and family history.[3,7,8]

Therefore, even though a diagnosis of pulmonary embolism was initially reached, not all clinical and radiological findings were solely explained by this disease, and there may be situations where multiple diseases contribute to the overall clinical presentation. In this case, not only was there pulmonary embolism but also cardiac amyloidosis, explaining all the findings of right heart failure and imaging studies. More prevalent differential diagnoses, such as acute coronary syndrome, were ruled out based on history and magnetic resonance imaging.

Magnetic resonance confirmed the findings observed in the echocardiogram and also showed global late gadolinium enhancement and alteration of the inversion time sequence in myocardial blood. Myocardial scintigraphy with technetium demonstrated lower uptake compared to bone. This result is suggestive of light chain amyloidosis, especially when there are associated hematological changes, as transthyretin involvement typically results in higher myocardial uptake. Although scintigraphy was performed for this patient, its most relevant indication is to confirm the diagnosis of ATTR cardiac amyloidosis when serum proteins are in the normal range without the need for the gold standard biopsy exam.[3,7,8]

Typically, the detection of immunoglobulins in serum and urine protein electrophoresis and immunofixation indicates the need for further investigation with a bone marrow biopsy for a definitive diagnosis of light chain amyloidosis and the associated blood dyscrasia causing heart disease. A bone marrow biopsy should be accompanied by a tissue biopsy to identify amyloid fibers. Initially, since the disease has a systemic involvement, a biopsy can be performed at a more accessible location, such as subcutaneous tissue. However, in this case, as the biopsy was inconclusive, an endomyocardial biopsy was performed.[3,7,8] Thus, multiple myeloma initiated the entire disease process, with a manifestation of pulmonary embolism, as well as the excessive production of light chain antibodies from the plasma cells infiltrating the heart, resulting in heart failure.

In light chain amyloidosis, treatment should specifically target resolving the underlying hematologic condition, which is achieved through immunotherapy, chemotherapy, and autologous bone marrow transplantation. However, for bone marrow transplantation to occur, the patient must be in favorable clinical conditions to withstand the severity of onco-hematological treatment. In this case, the patient was in INTERMACS 3 – an advanced stage of the disease – stage 4 according to the Mayo Clinic staging for light chain amyloidosis, and therefore, he could not undergo intervention immediately. Furthermore, assessing the extent of disease involvement in multiple organs is crucial, as multiple organ failure stages make multiple organ transplants unfeasible. This patient only presented with cardiac manifestations of amyloidosis. Therefore, the therapeutic approach proposed was to administer chemotherapy to control the hematological disease and evaluate the response while awaiting heart transplantation. Once the heart transplant has been successfully performed, the next step would be the definitive treatment of autologous bone marrow transplantation to prevent multiple myeloma from deteriorating the transplanted graft.[8-10]

In general, the indication of heart transplantation for light-chain amyloidosis is a treatment reserved for very carefully selected cases. Few documented case series have been successful with heart transplants in these circumstances, given the demand for highly skilled medical and multi-professional teams in specialized hospital centers and their complexity. Involvement of multiple organs by the disease usually precludes heart transplantation most of the time. The mortality rate on the transplant waiting list is considerable and higher than for other etiologies. The recurrence rate of monoclonal gammopathy, which contribute to recurrent heart disease, remain elevated. In the long term, outcomes still fall below average compared to patients transplanted for other etiologies, despite considerable improvement over the years with the refinement of chemotherapy and the recommendation for autologous bone marrow transplantation to reduce disease recurrence.[9]

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Ethical guidelines

The patient has signed an authorization form to access his health information. The project has been submitted to *Plataforma Brasil* and approved by the institution's research ethics committee (*Sociedade Beneficente Israelita Albert Einstein*). Approval number (CAAE – *Certificado de Apresentação de Apreciação Ética*): 71148523.9.0000.0071.

Author Contributions

Conception and design of the research: Mangini S, Bacal F; Acquisition of data: Drummond TQ, Bacal F; Analysis and interpretation of the data: Drummond TQ, Trevizan LLB, Mangini S, Bacal F; Obtaining financing: Drummond TQ; Writing of the manuscript: Drummond TQ, Trevizan LLB; Critical revision of the manuscript for content: Trevizan LLB, Mangini S, Bacal F.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Sociedade Beneficente Israelita Brasileira Albert Einstein under the protocol number CAAE: 71148523.9.0000.0071. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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