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The challenge of clinical diagnosis of cardiac amyloidosis: Case report and literature review

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ABSTRACT

Introduction: Cardiac amyloidosis is a disease caused by the deposition and extracellular accumulation of defective proteins (amyloids) in the myocardium, which can lead to conduction disorders, diastolic dysfunction, and restriction to ventricular filling resulting in reduction of systolic volume and of cardiac output.

Case Report: The patient, a 62-year-old male with a history of ischemic stroke for two months, was referred to the outpatient clinic for investigation of thrombophilia due to echocardiographic changes suggestive of cardiac amyloidosis.

Conclusion: Cardiac amyloidosis is an underdiagnosed disease, and its early diagnosis is crucial for a better prognosis.

Keywords: AL amyloidosis, Cardiac amyloidosis, Diagnostic challenges, Monoclonal gammopathy

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INTRODUCTION

The pathogenesis of amyloidosis involves a failure in the control mechanisms responsible for intracellular degradation of misfolded proteins. It is known that an abnormally folded protein will not function properly due to the instability generated by its improper format, so cells have mechanisms to detect and destroy such errors. Nevertheless, those mechanisms can sometimes fail, leaving the ill proteins to persist for enough time to associate in the intra- or extracellular space, and even deposit in different tissues. The excessive accumulation of these deposits, the amyloids, is what eventually causes the dysfunctions seen amyloidosis [1].

Cardiac amyloidosis is a rare disease caused by the deposition of amyloids in cardiac tissue. There are many proteins which can be deposited, causing different subtypes of amyloidosis, but the two main ones are: light-chain (AL), which involves an abnormal immunoglobulin produced by plasma cells; and transthyretin (ATTR), which is caused by the deposition of a misfolded protein derived from the liver. The physiopathology course with myocardial infiltration, which thickens the ventricular walls, thus leading to concentric remodeling and a lower cardiac output. Consequentially, atrial pressure is raised, and atrial dilation follows. Additionally, intramyocardial vessels can also be infiltrated, compromising myocardial perfusion. The conduction system can also be affected, leading to arrhythmias, atrial fibrillation, and delays in atrioventricular conduction [2].

Cardiac amyloidosis is an underdiagnosed disease, and due to its initially silent course, when diagnosed, it is often already in advanced stages. In fact, approximately one-fourth of patients die within six months of their diagnosis [2]. Though it is considered a rare disease, its real prevalence in the population could be higher

than previously thought, as its diagnosis is sometimes missed. An increasing number of studies reveal that this condition is neglected in favor of other more well-known pathologies [3]. Furthermore, among individuals with heart failure (HF) with preserved ejection fraction, autopsy data prove amyloid protein deposition in 32% of people over 75 years old [4].

This report aims to underscore the significance of early and precise diagnosis of cardiac amyloidosis, a condition often overlooked but with profound implications for patients' well-being. Through a detailed clinical case presentation, it illustrates the hurdles met by healthcare professionals in finding and managing this disease. Furthermore, the report synthesizes current literature to offer a comprehensive insight into best practices and diagnostic methodologies, with the overarching goal of enhancing early detection and improving patient outcomes. Recent advancements have notably revolutionized the landscape of cardiac amyloidosis management. These include advancements in diagnostic techniques such as cardiac magnetic resonance imaging (MRI) and biomarker use, enabling more exact and prompt detection. Additionally, targeted therapies like transthyretin stabilizers and chemotherapy combined with autologous stem cell transplant have shown promise in slowing disease progression. Multidisciplinary collaboration among various medical specialties ensures an integrated approach to patient care, while education initiatives aimed at both healthcare professionals and patients enhance awareness and adherence to treatment protocols. Ongoing research endeavors and participation in clinical trials continue to drive innovation, standardizing care and improving treatment efficacy for individuals affected by cardiac amyloidosis. Thus, this report not only underscores the importance of early diagnosis but also highlights the transformative impact of recent innovations, offering valuable insights into the best management of this complex condition.

CASE REPORT

A 62-year-old male patient with a history of ischemic stroke two months prior to assessment was referred for thrombophilia evaluation. At the medical appointment, he presented with an echocardiogram (ECHO) and a cardiac MRI that were suggestive of amyloidosis. The exams revealed left ventricular dysfunction, with mildly decreased function, diffuse subendocardial late enhancement, and hypertrophy with septal predominance, with maximum myocardial thickness of 18 mm. No signs of dynamic obstruction were seen in the left ventricular outflow trac (Figure 1). At physical examination, he appeared fit, without visceromegaly at palpation or abnormal sounds at cardiac auscultation; that were also no macroglossia or neurological abnormalities. The patient presented on the electrocardiogram (EKG) an atrial flutter and low voltage QRS. The recorded heart rate was 65 bpm and systemic blood pressure was 90 × 60 mmHg. Laboratorial tests showed the presence of a lambda monoclonal part (without correlation with IgG, IgM, or IgA). The serum protein electrophoresis showed a normal pattern, negative serologies, as well as normal levels of aspartate aminotransferase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GT), alkaline phosphatase and bilirubin (Table 1). Serum immunofixation showed the presence of IgG/lambda. The serum free light chain showed a kappa/lambda ratio of 0.033, confirming the predominance of the monoclonal lambda chain (Table 2).

Bone marrow immunophenotyping: The sample collected consisted of a heterogeneous population, of which 18.55% were erythroblasts, 62.39% were granulocytes, 3.78% were monocytes, 6.46% were plasma cells, and 8.02% were lymphocytes. Of the lymphocytes, 66.70% were T cells (CD4/CD8: 1.76), 19.89% were NK cells, and 13.41% were B cells (kappa/lambda: 1.15). 98.10% of the plasma cells (6.34% of the total cells analyzed) expressed CD27, CD38, CD45 (weak), CD56, CD138, and lambda light chain restriction (cytoplasmic), with no expression of CD19 or other markers evaluated. Therefore, the immunophenotypic study shows bone marrow aspirate with 6.34% of plasma cells with abnormal immunophenotype and monoclonal expression of lambda light chain (cytoplasmic). Biopsy of bone marrow and abdominal fat samples confirmed the presence of amyloid protein with positive Congo red.

Table 1: Laboratory tests of diagnosis

Test	Result
Beta 2 microglobulin	4.68 mcg/mL
PT	13 s
aTTP	35 s
Fibrinogen	324
Factor VIII	87%
Ristocetin cofactor	144%
VWF	126%
LDH	98
Creatinine	34 mg/dL
Urea	0.72 mg/dL

PT: prothrombin time; a TTP: partially activated thromboplastin time; VWF: Von Willebrand factor; LDH: lactic dehydrogenase

Table 2: Kappa/lambda light chain free and pro-B type natriuretic peptide (BNP)

Test	Result ate diagnostic date	Result after treatment
Kappa	21.4 mg/L	14.4 mg/mL
Lambda	641 mg/L	208 mg/L
Kappa/lambda ratio	0.033	0.396
proBNP	4,522 pg/mL	1,468 pg/mL

DISCUSSION

The diagnosis of amyloidosis is still considered a major challenge for general clinicians, especially because it is not yet standardized. However, its understanding and early detection, both by specialists such as cardiologists and generalist physicians, correlate directly with better prognosis and increased patient survival. An international consensus document on AL amyloidosis defines histological diagnostic criteria through positive endomyocardial biopsy for cardiac amyloidosis with Congo red staining. In addition, confirmed extracardiac biopsy with AL amyloidosis and typical cardiac imaging characteristics or abnormal cardiac biomarkers (age-adjusted NT-proBNP or abnormal troponin T/I/Hs-troponin) should also be presented [5].

Clinically, the diagnosis of AL amyloidosis is associated with vague and nonspecific symptoms, such as fatigue, perineal edema, weight loss, exertional dyspnea, and orthostatic hypotension. It is also rare to see more specific clinical signs, such as macroglossia and periorbital purpura. Thus, due to the imprecise clinical characteristics, AL amyloidosis is often underdiagnosed compared to other well-known diseases. In line with these facts, the patient in this study did not present the disease defining clinical aspects upon history taking and physical examination.

There are two sets of patients for which suspicion of cardiac amyloidosis may arise: Those with HF due to the systemic form of deposition disease; and those who, based on earlier cardiac investigations, have ruled out other cardiac diseases. In such scenario, further corroboration comes from clinical findings of thrombophilia and thickening of the septal membrane found on echocardiogram [6]. The diagnostic criteria include a left ventricular wall thickness greater than 12 mm—in the absence of an earlier history and diagnosis of systemic arterial hypertension (SAH); and echocardiographic characteristics, such as decreased ventricles, ventricular dilation, pericardial effusion, and restrictive cardiomyopathy pattern [6]. In the case under discussion, it was possible to see features suggestive of cardiac amyloidosis via cardiac magnetic resonance (Figure 1). There was left atrial dilation; mildly decreased left ventricular systolic function; and left ventricular hypertrophy (reaching 18 mm thickness) with septal involvement.

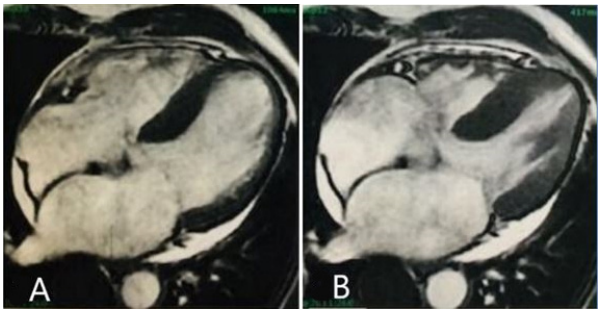

Figure 1: Cardiac magnetic resonance (A and B) showing septal hypertrophy (18 mm), an effect of cardiac amyloidosis (AL).

Low-cost tests such as the EKG and ECHO can bring amyloidosis into the investigative scenario provided that the physician is aware of this pathology [7, 8]. The EKG of patient in this study showed chronic atrial fibrillation or flutter. This exam, being a non-invasive method, is still considered a good aid in proving the diagnosis if it shows characteristics of low voltage (decreased progression of precordial leads) associated with left ventricular wall thickening [9, 10]. The diagnosis may be reached with 79% sensitivity and nearly 100% specificity, if the following combination is found: ECG showing low voltage QRS complex, axis deviation, and bundle branch blocks; and a left ventricular hypertrophy at the ECHO [7–10].

Other suggestive findings include [7, 8]:

1. Left ventricular wall thickness greater than 12 mm without a history of SAH;
2. Biatrial enlargement while preserving ventricular size;
3. Restrictive cardiomyopathy pattern with pericardial effusion and diastolic dysfunction.

In the face of abnormalities in EKG and ECHO, complementary tests may be necessary for diagnosis confirmation and establishment of amyloid subtypes. Useful possibilities include renal function status, magnetic resonance imaging, abdominal fat aspirate, and molecular imaging exams [11]. In cases of AL-type amyloidosis, bone marrow biopsy and immunohistochemical staining analysis are essential to reveal a clonal population of plasma cells responsible for producing defective light chains [6].

It is necessary for professionals to consider amyloidosis as a possible diagnosis in the presence of cardiological indications, precisely, because cardiac problems are the main cause of death in this population. For the establishment of the best therapeutic modality, some criteria are essential for staging and scoring, namely: NT-proBNP (<1,800 ng/L) [9, 10], troponin (T<0.025 ug/L), and the difference between involved and uninvolved free light chains (<18 mg/dL). Based on these data, stages 1–4 are delineated, thus providing an expectation of better or worse prognosis. Stage 4, using the Mayo Clinic prognostic table, would be the worst, with a survival rate of less than one year.

Furthermore, amyloidosis may be considered an underdiagnosed disease because it has an indolent course and does not include the range of major differential diagnoses in the face of manifestations of HF. Thus, aortic stenosis, atrial fibrillation, vagal bradycardia, sustained ventricular tachycardia, and atrioventricular block may obscure the prevalence of amyloidosis [11]. Nonetheless, the delay in setting up amyloidosis as a likely condition and initiating investigations has negative repercussions on the patient's prognosis, who could have access to modifier treatments earlier. Therefore, suspicions of cardiac amyloidosis can be raised with the aid of "Red flags" (Table 3), helping an early diagnosis and access to disease modifier treatments [11, 12].

Table 3: Warning signs for investigation of cardiac amyloidosis

When to suspect of cardiac amyloidosis?
CHF without etiology, LVH, ventricle without dilation
Patient with HCM and presence of pericardial effusion, AVB, septal thickening/valves, and granular appearance
Presence of LVH on ECHO and low voltage on EKG
>50 years with symmetric LVH without other factors such as SAH
Additional points from clinical history of HF due to amyloidosis: peripheral neuropathy, recurrent or bilateral carpal tunnel syndrome
Other signs and symptoms: orthostatic hypotension, macroglossia, thenar and hypothenar muscle wasting, bruises of unknown etiology

Abbreviations: CHF: Congestive heart failure; LV: Left ventricle; HCM: Hypertrophic cardiomyopathy; AVB: Atrioventricular block; LVH: Left ventricular hypertrophy; ECHO: Echocardiogram; EKG: Electrocardiogram; SAH: Systemic arterial hypertension; HF: Heart failure.

In the case of AL amyloidosis, it is important to bear in mind that treatment should be multidisciplinary, as this comorbidity can manifest in many different organs. In fact, the difficulty for an early diagnosis is partly due to its ability to affect multiple organs, with patients potentially seeking specialists in hematology, cardiology, nephrology, neurology, or hepatology. Thus, proper care is highly dependent on assessing which systems are involved and inviting help from specialists in those areas [6]. There are numerous treatment options for AL cardiac amyloidosis, with chemotherapy (CTx) being the most successful in terms of survival rates. The CTx used is the same as that employed in cases of multiple myeloma, with the central goal being to halt amyloid production through a proteasome inhibitor combined with cyclophosphamide, melphalan, and corticosteroids [9].

Overall, initially, it must be assessed whether the patient is suitable for autologous transplant, with cardiac function being a significant determinant. Among the Mayo Clinic criteria for transplantation are: Systolic BP > 90 mmHg, low troponins (<0.06 ng/mL), and functional class (NYHA) I/II. Patients who do not meet these criteria may face issues such as: the risk of cardiac arrest, for systolic pressure diminishes during treatment; and possible admission to the intensive care unit (ICU), as patients will endure a week of neutropenia and become unresponsive to vasoactive drugs during treatment.

It is also crucial to investigate tumor burden and signs of concomitant myeloma, with chemotherapy being shown prior to autologous transplant [9, 10, 12]. Given the comprehensive diagnostic investigation needed for cardiac amyloidosis, which incurs significant costs to public health, it is imperative for healthcare professionals to conduct an effective assessment and treatment. Keeping this disease in mind, particularly the warning signs and clinical history, will guide the request for complementary tests and, fundamentally, early therapy [13].

CONCLUSION

Cardiac amyloidosis is an underdiagnosed disease, for which an earlier recognition would result in great benefits for patients. Additionally, the difficulty in diagnosis exists because this disease is often not seriously considered as a differential diagnostic hypothesis. Thus, for patients with restrictive HF and left ventricular hypertrophy without another clear cause, it pays to remember the possibility of amyloidosis. Therefore, this article presents warning signs for the investigation of amyloidosis, as well as the proper investigative repertoire to be followed in a suspicious case.

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Author Contributions

Flávia Zattar Piazera – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Lucas Dornas Xavier – Conception of the work, Design of the work, Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Natalye Wynona Rosário Cunha – Conception of the work, Design of the work, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.