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Light-chain cardiac amyloidosis, a condition to consider in daily practice

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Abstract
AL-Amyloidosis is caused by a dysregulated plasma cell clone that produces light chains with a propensity to misfolding and deposition in the target organs. Cardiac involvement in AL amyloidosis is present in up to 70% of cases.
We present the case of a 76-year-old woman with a history of surgery for bilateral carpal tunnel syndrome, who presented to the emergency department with a clinical picture of decompensated heart failure. The electrocardiogram showed a low voltage in the limb leads discordant with left-ventricular concentric hypertrophy on the transthoracic echocardiography (TTE). Additionally, TTE demonstrated signs of diastolic dysfunction, mild pericardial effusion, as well as apical sparing on the peak longitudinal strain polar map. The ejection fraction was at 53%. A diagnosis of cardiac amyloidosis was suspected.
Serum Kappa and lambda free light chains were elevated with a ratio of 0,02. On nuclear scintigraphy and SPECT, there was no myocardial uptake of the radiotracer Tc99th HMDP.
Given the presence of renal involvement consisting of a nephrotic syndrom, the kidney was our biopsy site of choice. The anatomopathological study of the renal biopsy confirmed the diagnosis of AL-amyloidosis. A bone marrow aspirate ruled out concomitant multiple myeloma.
For management, the patient received guideline directed medical therapy for HFpEF, along with disease specific therapy consisting of chemotherapy with bortezomib, cyclophosphamide and dexamethasone.
Our case highlights the importance of integrating cardiac and extracardiac signs in raising the suspicion of cardiac amyloidosis and prompting specific investigations.

Keywords: Cardiac amyloidosis, light-chain, dysregulated plasma cell

Introduction
Systemic amyloidosis is a group of diseases characterized by Extracellular deposition of insoluble, misfolded fibrin in the form of B-pleated sheets that lead to organ dysfunction [1]. The two most common types of amyloidosis affecting the heart are light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis [2]. AL Amyloidosis is caused by a dysregulated plasma cell clone that produces light chains with a propensity to misfolding and deposition in the target organs [3]. Cardiac involvement in AL amyloidosis is frequent and can be demonstrated in up to 70% of cases. Our case highlights the importance of integrating electrocardiographic, echocardiographic and extracardiac signs in raising the suspicion of cardiac amyloidosis and prompting specific investigations.

Case Presentation
We present the case of a 76 years old woman with a history of surgery for bilateral carpal tunnel syndrome 3 years ago, who presented to the emergency department with worsening dyspnea and lower legs edema.
On physical examination, the patient was in moderately altered status. She had dyspnea at rest. The blood pressure was at 130/85 mmHg, heart rate at 105 bpm, and respiratory rate at 22 breaths per minute. Pulmonary auscultation revealed bilateral crackles at the base, while cardiac auscultation was normal. She also had pitting edema of the lower limbs arriving at the ankles. The cutaneous examination revealed a periorbital hematoma (Fig. 1).

The electrocardiogram (ECG) showed sinus tachycardia at 120 beats per minute (bpm), a QS morphology in leads in V1 and V2, low voltage in the limb leads and premature atrial beats (Figure 2).

Transthoracic echocardiography (TTE) showed (figure 3) left ventricular concentric hypertrophy (interventricular septum thickness= 14 mm, posterior wall thickness = 14 mm) with a speckled appearance of the septum; There was regional hypokinesis of the basal segments with a preserved global systolic function (left ventricular ejection fraction (LVEF) at 53% using the Simpson biplane formula). Strain imaging was notable for altered Peak global longitudinal strain (PGLS) at -10, 6% with and apical sparing-pattern on the polar map (Figure 3-D). Additionally, there was severe diastolic dysfunction with a restrictive pattern on the mitral inflow and elevated Left ventricular filling pressures (Figure 3-C). The right ventricle was hypertrophied, with a normal systolic function. The inferior vena cava (IVC) was dilated at 24 mm. Tricuspid regurgitation estimated pulmonary systolic arterial pressure at 29 mmHg.

On laboratory testing, B-type natriuretic peptides (BNP) were 2150 pg/mL (cut-off for pathologic: > 100pg/mL), High-sensitivity Troponins Ic: 234 ng/L (reference range: <15 ng/L), Serum creatinine: 6,1 mg/L (reference range: 7-13mg/L), Albumin: 22g/L (reference range: 34-54 g/L), 24-hours urine protein: 5,45g/24h (reference range: 0-0,15g/24h).

For initial management, the patient received intravenous loop diuretics to alleviate signs of congestion, with a good clinical response.

Given the presence of heart failure with preserved ejection fraction (HFpEF), the hypertrophied LV on echocardiography discordant with the low QRS voltage on the ECG, the apical sparring on strain imaging, and the extracardiac signs (bilateral carpal tunnel syndrome, nephrotic syndrome and peri-orbital ecchymosis), we raised suspicion for cardiac amyloidosis, and immediately evaluated for the presence of free light chains in the serum and myocardial uptake of bone avid radiotracers on nuclear scintigraphy.

Serum Kappa free light chain was at: 21,76 mg/L (reference range: 3,3-19,4), and Serum Lambda free light chain was at:1020,4 mg/L (reference range: 5,71-26, 3) with a ratio of 0,02 (reference range: 0, 26- 1,65). On nuclear scintigraphy and SPECT, there was no myocardial uptake of the radiotracer Tc99th HMDP (Figure 4).

Given the nephrotic syndrome, a kidney biopsy was performed and demonstrated mesangial deposits, appearing as a green birefringence in polarized light after Congo red staining, immunohistochemical study revealed a Light chain precursor protein.

The diagnosis of Light-chain cardiac amyloidosis (AL-Amyloidosis) was immediately made.

A 24-hour Holter monitoring didn't record conduction or rhythm disturbances.

There was no evidence of concomitant multiple myeloma: the skeletal x-rays showed no signs of osteolytic lesions, the bone marrow aspirate didn't show significant plasma cell infiltration (<10% of nuclear elements) and the kidney biopsy didn't reveal signs of renal myeloma.

For management, the patient received guideline directed medical therapy for HFpEF, consisting of loop diuretics and aldosterone antagonist, along with disease specific therapy consisting of chemotherapy with bortezomib, cyclophosphamide and dexamethasone.

On 6-month follow-up, the patient had a complete hematologic response, with a normalization of the free light chains in the plasma, and regression of lower legs edema. However, she had residual stage II dyspnea with signs of hemodynamic congestion on echocardiography despite high doses of loop diuretics.

Discussion

It is important to recognize that cardiac amyloidosis is part of a systemic disease in which neurological, dermatological and/or renal involvement often coexists with cardiac involvement [3].

AL Amyloidosis is caused by a dysregulated plasma cell clone that produces kappa or lambda immunoglobulin light chain fragments that are prone to misfolding, aggregation, and deposition in the myocardial interstitium[3]. There are two mechanisms to the development of cardiomyopathy in AL amlyoidosis: the first is direct toxicity to cardiomyocyte [4], and the second is interstitial and/or perivascular amyloid fibril deposition that leads to disruption of tissue architecture inhibition of contractile/relaxation functions and microvascular dysfunction.

The critical step to enable a diagnosis of cardiac amyloidosis is clinical suspicion, based on orienting features, and forged by attention to extra-cardiac signs and symptoms.

We suspected cardiac amyloidosis in our patient due to the clinical presentation of HFpEF, hypertrophied LV on echocardiography discordant with the low QRS voltage on the ECG, the apical sparring on strain imaging, and the extracardiac signs consisting of nephrotic syndrome a history of bilateral carpal tunnel syndrome surgery; Witch are some of the features that have been proposed as red flags for clinical suspicion of cardiac amyloidosis [5].

The final common pathophysiologic pathway of cardiac amyloidosis of both AL and TTR subtypes is one of myocardial infiltration with subsequent progressive impairment in diastolic and systolic function that leads to heart failure. Other cardiac manifestations include: Conduction disease which may progress to complete heart block, atrial fibrillation and flutter [6], and angina due to coronary microvasculature compression [7]. We screened for rhythm disturbances in our patient through a 24-hour ECG recording, which only revealed premature supraventricular beats, without evidence of AV-bloc or atrial fibrillation.

Non-cardiac manifestations greatly increases recognition of AL-amyloidosis, and should be clinically investigated whenever there is echocardiographic evidence of increased wall thickness. These clinical features are numerous and follow organ system infiltration, including the kidneys (usually a nephrotic syndrome), soft tissues (macroglossia, carpal tunnel syndrome), gastrointestinal tract (bleeding), or nervous system (peripheral or autonomic neuropathy). Periorbital ecchymosis caused by capillary fragility is pathognomonic of AL amyloidosis and when present, can determine the subtype of cardiac amyloidosis. Our patient had periorbital ecchymosis, which was initially thought to be the result of a facial trauma she recently experienced.

ECG criteria include pseudo-infarct pattern, low QRS voltage, and conduction system abnormalities.

Echocardiography is usually the examination that raises suspicion of cardiac amyloidosis, and therefore, plays a

crucial role in the diagnostic pathway for cardiac amyloidosis identification[8]. Findings include increased biventricular thickening (usually above ≥12 mm for the LV), dilated atria, interatrial septal thickening, valvular thickening, evidence of right ventricular thickening, pericardial effusion, and diastolic dysfunction). Global measures of systolic function are generally preserved in early to midstage disease; however, segmental variation in systolic function is evident early. Global longitudinal strain is often reduced and a specific feature of the polar map is a of "apical sparing".

CMR has greater sensitivity than echocardiography to diagnose cardiac amyloidosis through the capacity to visualize the extracellular space expansion that results from amyloid fibril deposition, it had also the advantage to differentiate other diseases that mimic cardiac amyloidosis such as sarcomeric hypertrophic cardiomyopathy and Fabry disease [8].

Laboratory abnormalities include elevated brain natriuretic peptide, troponin, and biomarkers of specific organ involvement such as proteinuria. Free light chain detection is critical for diagnosis, and the following tests should be performed: serum kappa/lambda free light chain rate and ratio, serum protein immunofixation, and urine protein immunofixation.

Bone avid tracers scintigraphy helps to distinguish ATTR from AL amyloidosis, and usually doesn't show fixation in AL amyloidosis [9]. The presence of grade 2 or 3 scintigraphy in patients without monoclonal protein is 100% specific for ATTR amyloidosis [10].

To establish a diagnosis of AL amyloidosis, a histological confirmation is mandatory. This is because a study showed that 1 in 4 patients with TTR amyloidosis have elevated light chains in the plasma [11]. Myocardial biopsy is the "Gold Standard" [3], However, due its high-risk, it is performed as a second-line procedure when the biopsy of other sites is negative and the clinical suspicion of the diagnosis is high. Since our patient had evidence of kidney involvement presenting a nephrotic syndrome, we decided to perform a kidney biopsy, which led to the histological confirmation of AL-Amyloidosis.

Therapy for cardiac amyloidosis is based on supportive Non-disease modifying therapies which includes guideline directed management of heart failure, arrhythmia management, and organ transplantation, and on disease-targeted therapeutics.

Disease specific therapy for AL-amyloidosis is based on chemotherapy aimed at abolishing the amyloidogenic plasma cell dyscrasia, and the main regimen is bortezomib, cyclophosphamide, and dexamethasone [12].

The prognosis of AL amyloidosis depends on the stage of the disease at presentation and the response to chemotherapy. The stage of the disease was assessed for our patient using the mayo scoring system, which was a stage 3b, a marker of advanced disease with a median survival of 1 year [12]. Surprisingly, after 2 years of follow-up, our patient was only hospitalized once for decompensated heart failure precipitated by pulmonary infection and had only a stage II NYHA heart failure symptoms. This can be explained by our patient's complete hematologic response to chemotherapy and by the fact that this system is based upon survival after treatment with older therapeutic regimens and may not be relevant for patients treated with bortezomib containing combination therapies [13].

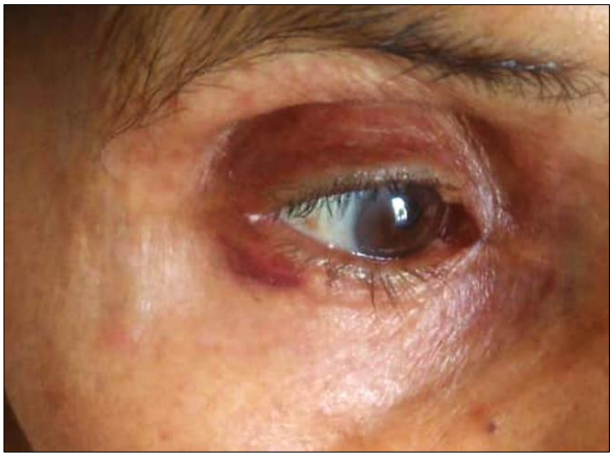

Fig 1: Photography of the patient showing a periorbital hematoma

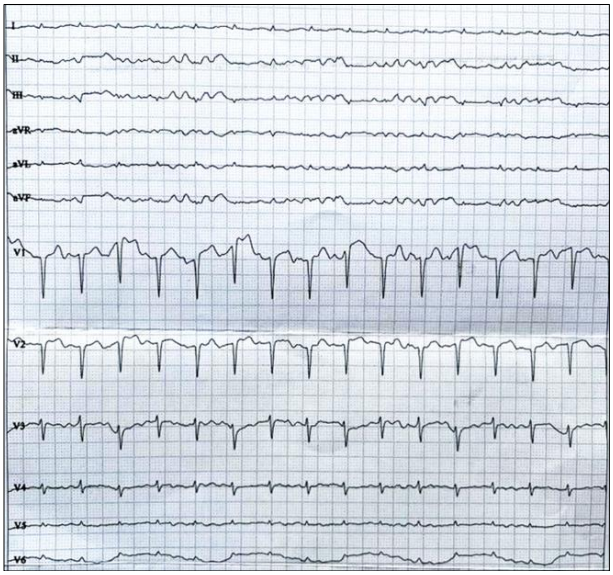

Fig 2: 12 Leads ECG showing a QS pattern in leads V1 and V2, and low QRS amplitudes in the limb leads

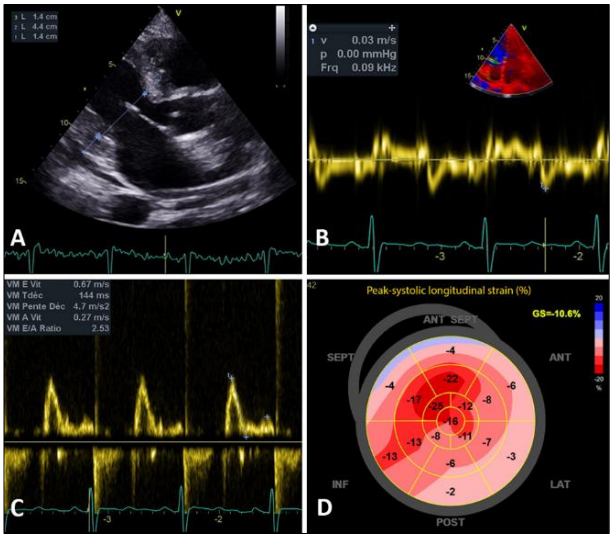

Fig 3: Transthoracic echocardiography findings. Panel A: Parasternal long axis view showing LV concentric hypertrophy. Panel B: severely impaired e' at the septal mitral annulus during tissu doppler imaging. Panel C: Restrictive mitral inflow pattern. Panel D: Altered global peak longitudinal strain with an apical sparing-pattern

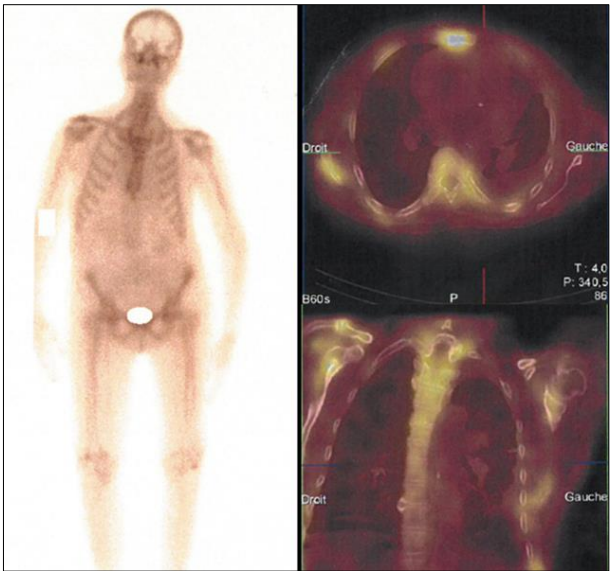

Fig 4: nuclear scintigraphy and SPECT showing the absence of myocardial uptake of the radiotracer Tc 99th HMDP

Conclusion

In the past decade, tremendous progress has been made in the diagnosis and treatment of all forms of amyloidosis, especially AL amyloidosis. This development has transformed the paradigm of cardiac amyloidosis from a rare and untreatable disease to a condition that cardiovascular clinicians should consider in daily practice.

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