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SCIENTIFIC LETTER

Multimodality imaging approach in light chain (AL) cardiac amyloidosis: a case report

Abordaje de imagen multimodal en amiloidosis cardiaca por cadenas ligeras (AL): reporte de caso

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Case presentation

Cardiac amyloidosis, (CA) despite being considered an unusual condition in the spectrum of heart diseases, has garnered increased attention and recognition in recent years. This is attributed to advancements in diagnostic techniques and a growing understanding of its clinical manifestations. It can affect multiple organs, including the heart, kidneys, liver, and autonomic nervous system. It is caused by the extracellular deposition of misfolded insoluble proteins. In > 98% of cases, it is attributed to the deposition of monoclonal immunoglobulin light chains (AL) or transthyretin (TTR), transthyretin amyloidosis variant, or transthyretin amyloidosis wild-type (ATTRwt). ATTRwt. However, roughly 75% of AL Amyloidosis patients experience cardiac involvement. Clinical symptoms, such as heart failure, arrhythmias, and restrictive cardiomyopathy, may initially overlap with other cardiac disorders, contributing to diagnostic delays, especially in older adults[1,2]. It is crucial to consider this condition in patients with suggestive systemic conditions; “red flags” are helpful in suspecting it, especially if compatible cardiac signs are observed, such as decreased QRS amplitude, noted in up to 64% of patients, myocardial thickening, or a bull’s-eye or Japan flag plot pattern on echocardiography, the latter obtained through longitudinal strain with a sensitivity of 93% and specificity of 82%[3,4]. The importance of this evaluation is highlighted by the fact that normal voltage in an electrocardiogram (ECG) and normal septal thickness have a negative predictive value of ~ 90%[5]. AL is one of the most rapidly progressive forms, with survival post-heart failure being < 12 months. Early diagnosis is essential, as prognosis largely depends on timely treatment initiation.

The aim of this case report is to explain in detail the clinical, electrocardiographical, and imaging approach in patients with AL CA.

A 73-year-old Hispanic man, without notable medical history, experienced asthenia, fatigue, worsening dyspnea, lower limb swelling, and hand paresthesia over 3 months. Subsequently, he developed orthopnea and generalized edema. A diagnosis of heart failure was made, and diuretic treatment resulted in partial improvement. However, resting dyspnea persisted, leading to his medical referral. Upon examination, macroglossia (Fig. 1A), periorbital ecchymosis (Fig. 1B), apical impulse in the sixth space, bilateral pleural effusion syndrome, and moderate lower limb edema were observed. Furosemide diuretic treatment was initiated, demonstrating improvement. The ECG showed low

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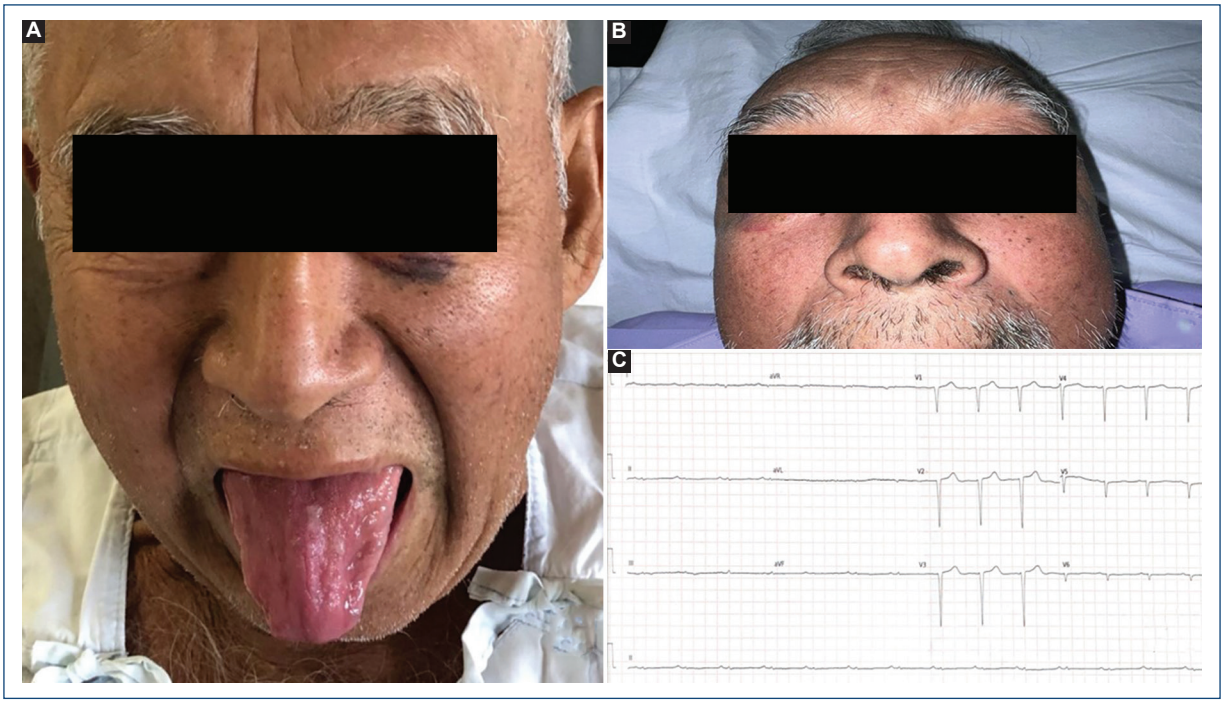

Figure 1. A: macroglossia. **B:** periorbital echymosis. **C:** electrocardiogram with low voltage complexes as well as pseudoinfarct pattern.

voltage complexes as well as pseudoinfarct pattern (Fig. 1C), cardiomegaly in the X-ray, and pleural effusion. Laboratory results indicated creatinine at 1.28 mg/dL, nephrotic-range proteinuria with hypoalbuminemia, mixed dyslipidemia, hyperuricemia, thyroid-stimulating hormone 11.8 with low T4, lactate dehydrogenase 275 U/L, B2 mg 3.58 mg/L, C-reactive protein 54.8 mg/dL, troponin T 16.7, and NT-proBNP 27347 pg/mL.

Considering the presence of numerous indicative signs of amyloidosis because of multiple organ-damage involvements, an echocardiogram was undertaken, uncovering marked myocardial hypertrophy (Fig. 2A and B), a septal mottled pattern, and biauricular dilation. In addition, distinctive bull's eye or Japan flag patterns (apical sparing) were discerned in strain imaging (Fig. 2C). To further enhance the diagnostic approach, cardiac magnetic resonance imaging (CMRI) was executed, revealing noteworthy myocardial hypertrophy, diffuse transmural late gadolinium enhancement in the right ventricular free wall, a left ventricular ejection fraction of 63%, right ventricular ejection fraction of 55%, mild pericardial effusion, and a substantial increase in extracellular volume of 71% (Fig. 2D and E), thereby satisfying diagnostic criteria through both modalities. Furthermore, to differentiate between AL and ATTR amyloidosis, we performed a 99m Technetium-pyrophosphate (99mTc-PYP) scan, resulting in absent myocardial uptake (Fig. 2F), discarding ATTR phenotype.

In this sense, protein electrophoresis and immunofixation were done showing a significant increase in Lambda chains and a positive Congo red staining biopsy of the fat pad. Primary amyloidosis due to light chain disease was diagnosed, and he was referred to hematology for the initiation of chemotherapy.

Discussion

CA leads to restrictive cardiomyopathy due to the extracellular deposition of various proteins in the myocardium. At present, over 30 proteins capable of forming amyloid fibrils have been identified. The most common ones involved are AL, stemming from abnormal clonal plasma cell proliferation, or TTR, a liver-synthesized protein associated with transporting thyroxine and retinol-binding protein[6]. Limited data exists in Latin America regarding amyloidosis incidence. A cohort study from the Hospital Italiano in Argentina reports an incidence of 11/1,000,000 patients per year for AL amyloidosis, with 60% presenting an important heart involvement[7].

In general, specific clinical, electrocardiographic, and echocardiographic findings, designated as "red flags,"

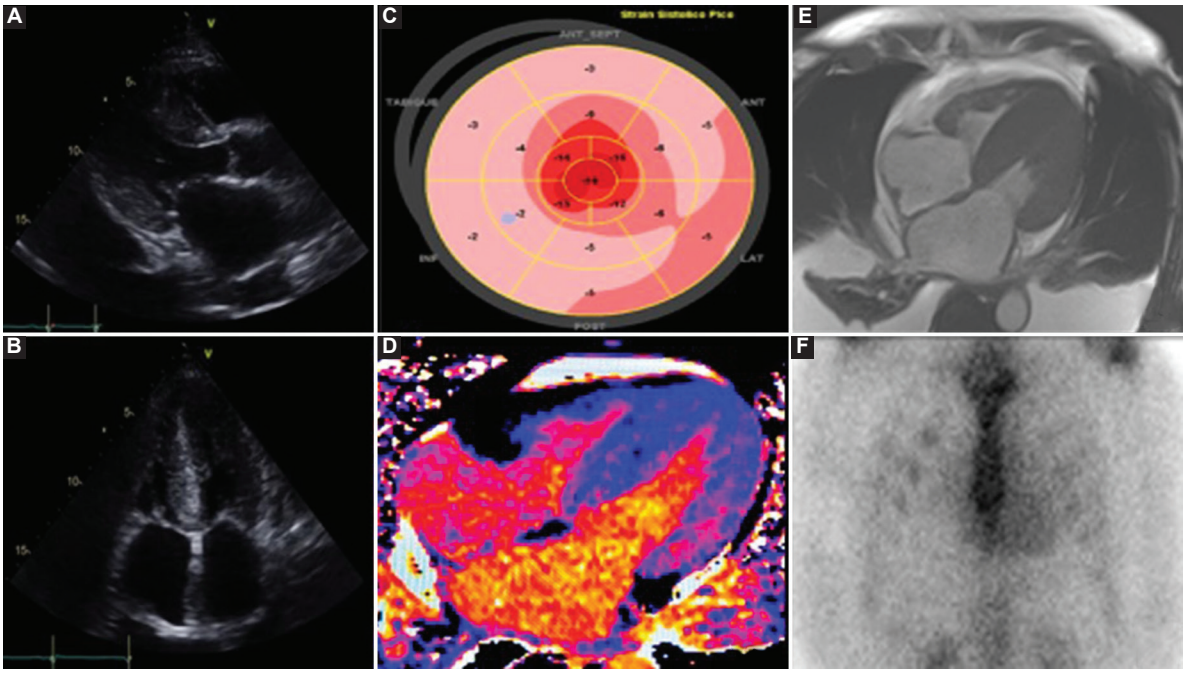

Figure 2. A: long-axis parasternal view in echocardiogram with marked myocardial hypertrophy. **B:** four-chamber view in echocardiogram with important septal hypertrophy, as well as rough, mottled pattern, and biauricular dilation. **C:** typical apical sparing in Strain imaging. **D:** T2 mapping with an increase in investment times, suggesting diffuse amyloidosis with high extracellular water/protein volume. **E:** cardiac magnetic resonance imaging with marked myocardial hypertrophy, diffuse transmural late gadolinium enhancement in the right ventricular free wall, mild pericardial effusion, and a substantial increase in extracellular volume. **F:** 99m technetium-pyrophosphate scan with absent myocardial uptake.

serve as pivotal indicators in suggesting a diagnosis of amyloidosis. These include polyneuropathy, skin bruising, macroglossia, ruptured biceps tendon, renal impairment, proteinuria, pseudoinfarct pattern, and left ventricular wall thickness exceeding 12 mm[2]. Our patient exhibited multiple of these significant indicators, prompting the continuation of amyloidosis screening. Consistent with our case, Carretero et al.[7] reported that individuals with AL amyloidosis had a median age of 64 years, predominantly male (53%), with the heart and kidneys being the primary organs affected. Cardiac involvement emerged as a crucial prognostic factor, contributing to a median survival rate of 6-12 months.

As per current guidelines for CA, the subsequent steps in the study protocol involve screening for the presence of a monoclonal light chain and simultaneous 99 mTc-PYP scan, strategically optimizing the timing of the approach. Our research team executed this protocol, revealing a negative single-photon emission computed tomography scan and a significant elevation in Lambda chains, effectively excluding ATTR amyloidosis. Nevertheless, in accordance with the findings of Wechalekar et al.[8], these results may indicate the presence of a monoclonal gammopathy of undetermined significance, multiple myeloma, indolent B cell lymphoma, Waldenström macroglobulinemia, or AL amyloidosis. Therefore, confirmation of the diagnosis necessitates Congo red staining of a tissue biopsy sample, a procedure that was conducted on our patient. In addition, CMRI can be incorporated into the CA diagnostic approach due to its capability to provide high-resolution structural and functional data, along with tissue characterization information. This proves particularly relevant when infiltrative cardiomyopathy is suspected but CA is less likely, or to rule out other phenocopies, including sarcoidosis, hemochromatosis, fabry disease, as well as hypertrophic cardiomyopathy, myocarditis, or constrictive pericarditis[6]. In addition, T2 mapping is useful in establishing prognosis in patients with CA; the greater the extracellular volume, the greater the mortality[9].

In the contemporary context, there is no single imaging modality that can perform a detailed diagnosis as well as assessment of the morphologic/functional consequences of CA. Consequently, the application of

multimodal imaging is essential for the clinical evaluation of CA, to differentiate the multiple phenotypes due to the different treatments they require and the different prognoses that each of them entails[9]. Beyond its diagnostic utility, the multimodality approach is acknowledged for its ability to furnish prognostic insights. Notably, factors such as left ventricular wall thickness exceeding 15 mm, right ventricular dysfunction, and hypertrophy are correlated with an adverse prognosis[10].

For all described above, the multimodality imaging approach in CA is essential, as well as the serum, urine biomarkers, and biopsy to identify the CA subtype.

In summary, CA is a progressively recognized disorder associated with a grim prognosis. It is imperative for cardiologists to be well-versed in recognizing potential indicators that raise suspicion of this disease. Initiating a comprehensive multimodality imaging approach and conducting key laboratory tests for identifying the amyloidosis phenotype are crucial steps in the diagnostic process.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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