

# Cardiac Amyloidosis: The Importance of a Multidisciplinary Approach

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Cardiac amyloidosis is associated with the interstitial deposition of abnormal protein in the myocardium, which can lead to a form of restrictive cardiomyopathy with a poor prognosis. This protein can have a number of different origins, which give rise to various subtypes of amyloidosis that have different prognoses and that require different therapeutic approaches. Drugs commonly used in heart failure have little effect in amyloidosis and the use of heart transplantation is controversial because amyloidosis is a multi-organ disease and because there is a possibility of disease recurrence in the graft.

The use of new techniques to identify the specific amyloidosis subtype, the emergence of novel ways of preventing or decreasing amyloid production, the ability to monitor responses to therapy and, above all, the introduction of multidisciplinary teams that can implement a combination of therapies, including multiple organ transplantation, have contributed to a substantial improvement in the prognosis of this disease.

**Key words:** Cardiac amyloidosis. Restrictive cardiomyopathy. Heart transplantation.

## Amiloidosis cardíaca: la importancia del manejo multidisciplinario

La amiloidosis cardíaca causa una miocardiopatía restrictiva de mal pronóstico debida al depósito intersticial de proteína anómala en el miocardio. Esta proteína puede tener diversos orígenes y dar lugar a subtipos de amiloidosis con diferente pronóstico y manejo terapéutico. Los fármacos utilizados habitualmente en la insuficiencia cardíaca son poco eficaces en la amiloidosis, y la indicación de trasplante cardíaco es controvertida porque la enfermedad afecta a múltiples órganos y por la probabilidad de recidiva en el órgano trasplantado.

La utilización de nuevas técnicas para la identificación del tipo de amiloidosis, la aparición de procedimientos capaces de impedir o disminuir la producción de amiloide, la posibilidad de monitorizar la respuesta al tratamiento y, sobre todo, la formación de equipos multidisciplinarios capaces de realizar tratamientos combinados, que incluyen el trasplante multiorgánico, han contribuido a mejorar sustancialmente el pronóstico de la enfermedad.

**Palabras clave:** Amiloidosis cardíaca. Miocardiopatía restrictiva. Trasplante cardíaco.

## INTRODUCTION

Cardiac amyloidosis (CA) is caused by deposition of an insoluble protein material, known as amyloid substance, in the cardiac interstitium. This abnormal protein can have different origins and molecular compositions, thus giving rise to different types of amyloidosis. CA can be part of a systemic disease

with involvement of other organs, or, more rarely, affect only the heart. The condition usually presents as a restrictive cardiomyopathy that leads to death from heart failure in most patients. The indication for cardiac transplantation (CTx) is controversial because of poor post-transplantation survival related to multiorgan involvement and the probability of recurrence in the transplanted organ. Fortunately, recent advances in the management of CA have improved the life expectancy of affected patients.

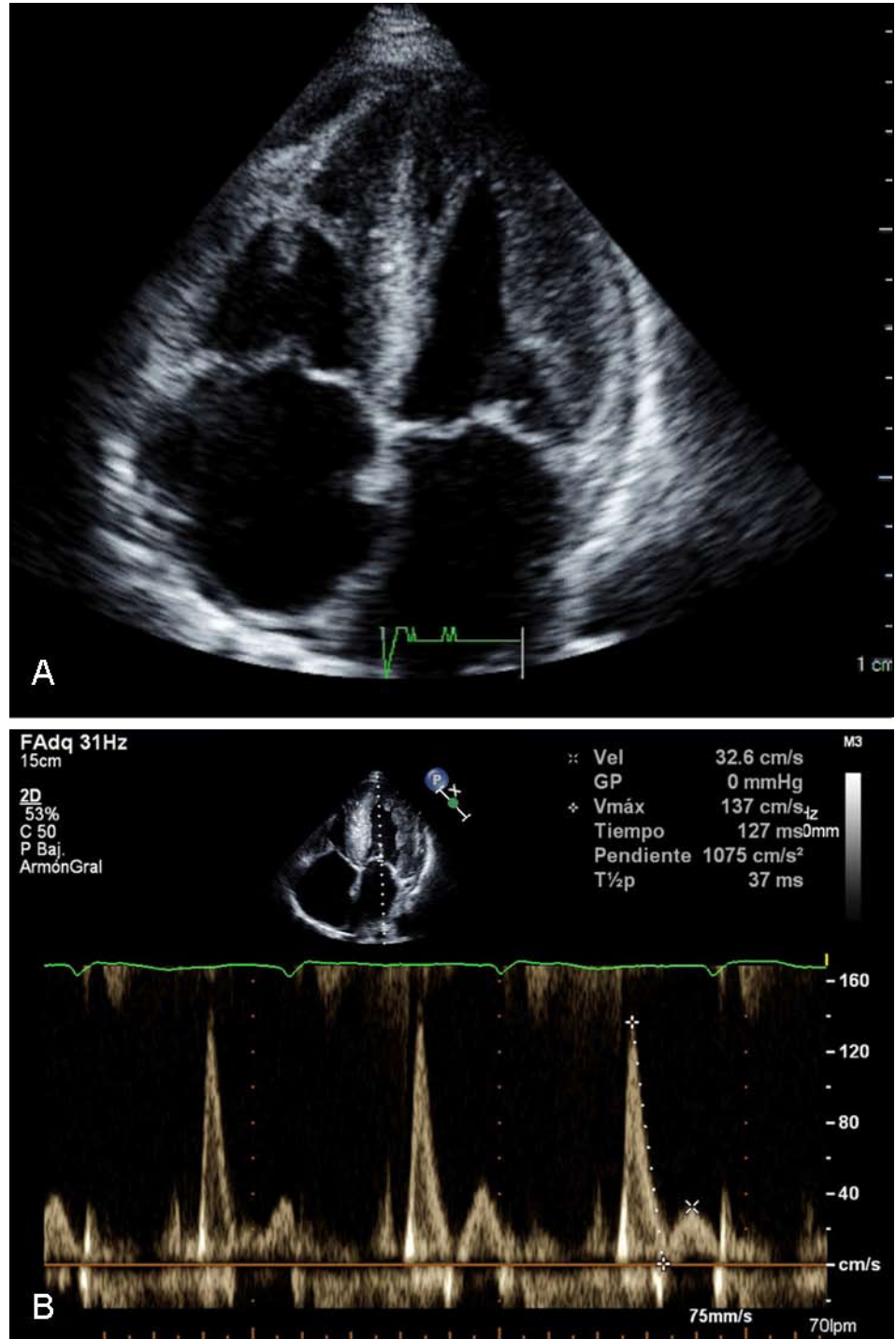
## METHODS

Three patients with CA evaluated in our unit during 2005 to 2007 are presented. All underwent combined treatments that included CTx.

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**Figure 1.** Echocardiogram from patient 1. A: dilatation of both atria with increased atrial septal thickness. Left ventricle shows wall thickening and increased echogenicity. Thickened valves. B: mitral Doppler shows evidence of severe restriction.

## RESULTS

### Patient 1

A 53-year-old man presented with dyspnea, asthenia, abdominal distension, evident jugular vein enlargement, third heart sound, hepatomegaly, ascites, and edema. Electrocardiography showed sinus rhythm and decreased voltages, and indicated

restrictive, infiltrative cardiomyopathy (Figure 1). Endomyocardial biopsy (EMB) confirmed the suspected diagnosis of CA, and bone marrow biopsy (BMB) demonstrated 8% monoclonal plasma cells, confirming the diagnosis of primary (AL) amyloidosis. Additional examinations excluded significant involvement of other organs.

Because of the patient's rapid hemodynamic deterioration, he required intra-aortic balloon



**Figure 2.** Explanted heart of patient 2. Both ventricles are thickened and show a pearly color that is more evident in the subendocardium. A pacemaker electrode is visible in the right ventricle.

counterpulsation until emergency CTx could be performed. Following a postoperative period initially complicated by renal failure, he was discharged in excellent clinical and analytical condition. At 7 months post-transplantation, autologous bone marrow transplantation (BMT) was performed, with a temporary reduction in immunosuppressive drugs to favor stem cell mobilization, which were infused 1 month later, following preparation with intravenous melphalan and prednisone. At discharge, the patient was asymptomatic and immunosuppressant concentrations were adequate, but 2 weeks later he died suddenly in his home. The autopsy showed severe cellular rejection in the heart graft.

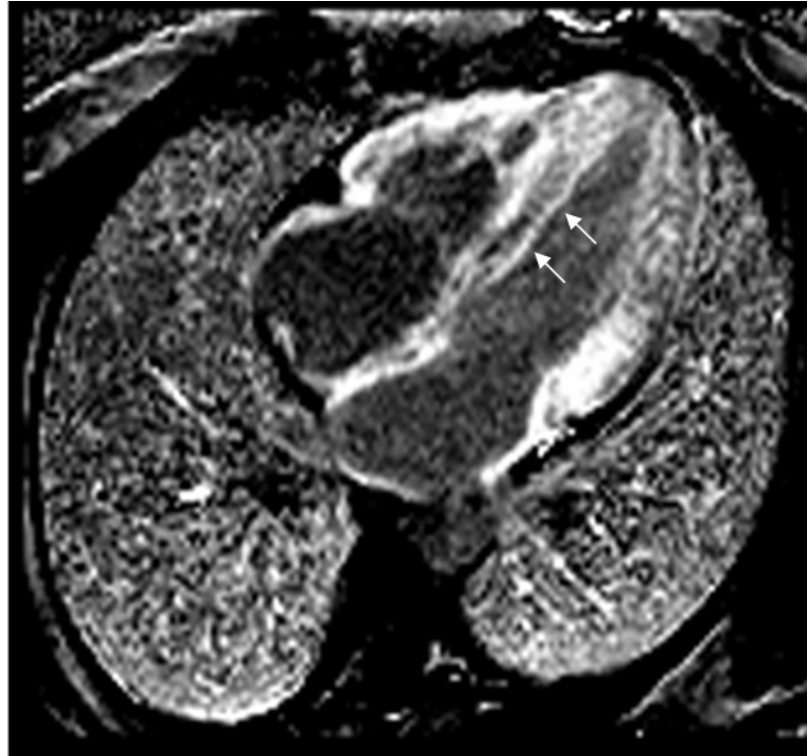
### Patient 2

A 52-year-old man with no family history of interest had a background of bilateral carpal tunnel syndrome and pacemaker implantation 4 years previously due to atrial fibrillation and a slow ventricular response. Two years later, because of an episode of heart failure, he underwent echocardiography, which was consistent with restrictive cardiomyopathy, and an abdominal fat biopsy with positive results, leading to the diagnosis of AL amyloidosis. Over the next 2 years, the patient presented with several episodes of orthostatic syncope and hospitalizations for heart

failure; hence he was referred to our hospital for CTx assessment.

The clinical signs and symptoms were not typical of primary amyloidosis because of the slow evolution, absence of a monoclonal peak in blood and urine, and a normal BMB, which raised the suspicion of another diagnosis. Scintigraphy with technetium-99m diphosphonate ( $^{99m}\text{Tc-DPD}$ ) demonstrated radioisotope uptake in the myocardium, and immunohistochemistry of EMB specimens showed transthyretin deposition. Genetic studies disclosed a heterozygous mutation (Glu89Lys) in the transthyretin gene, which established the diagnosis of familial amyloidogenic transthyretin (ATTR) amyloidosis (neuropathic amyloidosis). The evaluation included an electroneurogram, which evidenced moderate sensory-motor polyneuropathy.

Because of the patient's poor clinical evolution, he was included on the waiting list for a CTx, which was ultimately carried out without complications (Figure 2). Six months later he was placed on the liver transplantation (LTx) waiting list, where he remained for 1.5 years, during which time the EMB showed no amyloid and his neuropathy progressed slowly, without causing significant disability. Three years following CTx and 1 year after LTx, at the time of writing, the patient is able to maintain a normal lifestyle.



**Figure 3.** Magnetic resonance imaging in patient 3. Increased wall thickness and gadolinium enhancement is seen in the subendocardium of both ventricles, atria and septae, producing the “train track” sign (Courtesy of Drs M.A. Cavero and M. Pastrana).

### Patient 3

A 45-year-old woman consulted for a 4-month history of asthenia, dyspnea, and edema. The laboratory work-up was normal except for N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) values of 16 560 pg/mL, and echocardiography showed signs of restrictive cardiomyopathy. Gadolinium-enhanced magnetic resonance demonstrated a typical pattern of subendocardial enhancement (Figure 3). EMB study confirmed the presence of amyloid and the BMB showed 11% kappa chain-producing, CD56+ monoclonal plasma cells. Based on the diagnosis of AL amyloidosis, treatment with oral cycles of melphalan and prednisone was started, and the monoclonal plasma cell population disappeared in a few weeks. Despite this response, the patient underwent repeated hospitalizations for heart failure, NT-proBNP and troponin levels increased, and the echocardiogram showed deterioration of biventricular systolic function. After excluding significant involvement of other organs, treatment by double transplantation was decided.

The postoperative was prolonged because of recurrent pleural effusions, and the patient was discharged 40 days later. Six months after the procedure, the patient was hospitalized for bone marrow transplantation (BMT), but sufficient stem cells could not be mobilized. Because of the absence of paraprotein and pathologic plasma cells in the

bone marrow, we decided on follow-up monitoring and treatment with bortezomib, and/or a new attempt at BMT, depending on the evolution. One and a half years after CTx, the patient’s clinical status was excellent, the heart graft showed no evidence of amyloid, and there were no light-chain immunoglobulins in plasma or monoclonal plasma cells in BMB specimens.

### DISCUSSION

In primary or AL amyloidosis, the amyloid substance is formed by light chains of immunoglobulins produced by plasma cell dyscrasia. Although the infiltration usually affects several organs, the heart is involved in more than 50% of cases and this implies a devastating prognosis, with a median survival of 6 months following the diagnosis. Support treatment for the associated heart failure is based on diuretics. Angiotensin-converting enzyme inhibitors and beta-blockers are poorly tolerated in patients with symptomatic hypotension, and calcium channel blockers are not advisable because of their tendency to bind with the anomalous protein.<sup>1</sup> Treatment directed against the plasma cell clone can halt protein deposition and even revert the deposits already formed, in addition to improving function of the affected organs. The most commonly used drugs for this condition are melphalan and prednisone, although

others such as vincristine, lenalidomide, rituximab, and bortezomib (proteasome inhibitor that reduces amyloid synthesis) have shown variable usefulness.<sup>2</sup> BMT achieves the best response, but this measure is inadvisable in patients with advanced heart disease.<sup>3</sup> In selected cases, and at centers with experience, the most widely accepted strategy is to first perform CTx (assuming it will be a high-risk transplant, as in our 2 patients) and then administer etiologic treatment for the amyloidosis (chemotherapy and/or BMT). Survival is less than 5 years in patients who do not receive specific treatment following CTx, with death being due to failure of other affected organs or to recurrent graft amyloidosis.<sup>4</sup>

Bone marrow transplantation in patients with a CTx carries additional risks, related in part to the difficulty of maintaining a stable level of immunosuppression, as occurred in our first patient, who died due to severe rejection 9 months following CTx despite close, regular EMB monitoring and echocardiography. In contrast, in patient 3, BMT was impeded because of immunodeficiency, but the response to chemotherapy was so favorable that 1.5 years after the last dose there were no signs of circulating amyloid. The possibility to detect free chains of immunoglobulins that are amyloid precursors facilitates monitoring of the disease and allows treatment to be individualized. Should the paraprotein reappear in our patient, the therapeutic options include various drugs, and autologous or allogeneic BMT.

ATTR amyloidosis, also known as Corino-Andrade disease or familial neuropathic amyloidosis, is produced by an anomalous variant of transthyretin or prealbumin, a protein that originates in the liver and is mainly deposited in the heart and nervous system. More than 100 different mutations causing ATTR have been recognized. Depending on the type of mutation, the disease mainly affects the heart, nervous system, or both organs.<sup>5</sup> Although the echocardiographic findings at the time of the diagnosis are indistinguishable from those of AL amyloidosis, the progression of ATTR is slower, and mean survival of the affected patients is longer. <sup>99m</sup>Tc-DPD cardiac uptake in ATTR can aid in differentiating this condition from other types of amyloidosis.<sup>6</sup> Anti-inflammatory drugs such as

diflunisal achieve stabilization of transthyretin and prevent amyloid formation in vitro.<sup>7</sup> Nonetheless, in clinical practice, there is no specific treatment for this type of amyloidosis, apart from CTx in cases of advanced heart failure and LTx to eliminate the amyloid-producing organ (patient 2). Identification of carriers of the anomalous gene in family members of patients with ATTR can enable LTx to be performed in the early, initial phase of heart or nervous system involvement.

There are other types of amyloidosis, such as secondary or AA amyloidosis, which appears in situations of chronic inflammation and usually does not affect the heart, and senile amyloidosis, which is rare in patients younger than 60 and is not generally treated with CTx.

In conclusion, the development of techniques to identify the type of CA and monitor the response to treatment, the development of drugs able to decrease amyloid production and favor regression of existing deposits, and above all, the formation of multidisciplinary teams specialized in the management of this type of disease, which includes multiple organ transplantation, open a door to hope for the future in patients with AC.

## REFERENCES

1. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation*. 2005;112:2047-60.
2. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. *J Am Coll Cardiol*. 2007;50:2101-10.
3. Lacy MQ, Dispenzieri A, Hayman SR, Kumar S, Kyle RA, Rajkumar SV, et al. Autologous stem cell transplant after heart transplant for light chain amyloid cardiomyopathy. *J Heart Lung Transplant*. 2008;27:823-9.
4. Dubrey SW, Burke MM, Hawkins PN, Banner NR. Cardiac transplantation for amyloid heart disease: the United Kingdom experience. *J Heart Lung Transplant*. 2004;23:1142-53.
5. Suhr OB, Svendsen IH, Andersson R, Danielsson A, Holmgren G, Ranløv PJ. Hereditary transthyretin amyloidosis from a Scandinavian perspective. *J Intern Med*. 2003;254:225-35.
6. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using <sup>99m</sup>Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol*. 2005;46:1076-84.
7. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. *Amyloid*. 2006;13:236-49.