Unusual high 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) tracer deposition on a heart scintigraphy in a patient with AL amyloidosis: A case report

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We present a case of a 40-year-old Spanish man with cardiac amyloidosis in which a Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-99m-DPD) scintigraphy was strongly suggestive of cardiac amyloidosis by transthyretin (ATTR) but endomyocardial biopsy (EB) analyzed by immunohistochemistry demonstrated a light chain amyloidosis (AL). Even though the Tc-99m-DPD has proven in different published papers that has high sensibility and specificity for differentiating AL and ATTR cardiac amyloidosis, we present an unusual case of an AL cardiac amyloidosis with a Perugini grade 3 on the scintigraphy. Diagnostic approach of cardiac amyloidosis following consensus documents is discussed to avoid diagnostic mistakes based on imaging techniques.

Key Words: Amyloidosis • cardiac amyloidosis • scintigraphy • nuclear imaging • MRI

See related editorial, pp. 1126–1127

INTRODUCTION

Amyloid diseases are a group of pathologies characterized by deposition of proteinaceous substance, the amyloid fibril protein, on different tissues.[1] Organs affected by deposition of these proteins varies depending on the fibril type, with more than 36 amyloid fibril proteins described in humans (and other 10 in vertebrates animals),[2] but heart involvement is seen basically in three of them: light chain amyloidosis (AL, due to plasma cells dyscrasias), transthyretin amyloidosis (ATTR, in its senile [wild-type] or the familial [mutated] forms), and the serum amyloid A (AA, secondary to inflammatory diseases).[1,2]

The age of onset differs depending on the amyloid disease type, being the mean age of 60 years for the AL form, 51 years for the ATTR mutated (ATTRm), 75 years for the ATTR wild type[3] and a median age of 50 years for the AA form.[4] The AL type usually has a slightly increased wall thickness but has the most severe diastolic dysfunction and worst prognosis, while the ATTR forms have markedly increased wall thickness, less diastolic dysfunction, and less aggressive course.[3]

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Table 1. The most relevant laboratory work-up results are shown (emergency room and during in patient)

Laboratory test	Value	Normal reference value
Complete blood count		
Red blood count ($\times 10^6$)	5.47	4.05-6.00
Hemoglobin (g/dL)	15.3	13.00-18.00
Leucocytes ($\times 10^3$)	9.24	4.00-10.00
Neutrophils (%)	58.7	40%-85%
Platelets ($\times 10^3$)	181	130-400
Coagulation		
Prothrombin time (seg)	13.0	9.0-15.0
Prothrombin time (%)	82	65-125
Partial activated thromboplastin time (seg)	30.9	20-40
I.N.R.	1.14	0.80-1.40
Biochemistry		
Glucose (mg/dL)	91	70-110
Urea (mg/dL)	41	10-50
Creatinine (mg/dL)	1.36	0.7-1.20
Serum ionic sodium (mmol/L)	143	136-145
Serum ionic potassium (mmol/L)	4.3	3.4-4.5
Creatine kinase (U/L)	61	20-200
Ultrasensible Troponin T (ng/L)	114	< 14.
NT-proBNP (pg/mL)	2,433	< 300
Alkaline phosphatase (U/L)	53	40-130
Aspartate aminotransferase (U/L)	16	0-40
Alanine aminotransferase (U/L)	17	0-41
Gammaglutamiltransferase (U/L)	30	0-60
Total Bilirubin (mg/dL)	2.8	0.1-1.2
Direct bilirubin (mg/dL)	0.8	0.0-0.3
Reactive C Protein (mg/dL)	0.2	0-0.5
Complementary lab test		
A1C-glycohemoglobin (%)	4.9	< 6.5
TSH (mU/L)	3.32	0.25-5.00
Serum iron (μg/dL)	46	59-158
Ferritin (ng/mL)	143	30-400
Transferrin (mg/dL)	246	200-360
Transferrin saturation index (%)	10	16-45
B2-microglobulin	3.2	< 2.2
Serum protein electrophoresis		
Albumin (g/L)	41.9	40.2-47.6
Alpha 1	3.4	2.1-3.5
Alpha 2	8.4	5.1-8.5
Beta	7.3	6.0-9.4
Gamma	8.1	8.0-13.5
Monoclonal peak	4.0	Absent
Total serum proteins (g/L)	60	64-83
Serum immunofixation		
Free kappa	22.24	3.30-19.40
Free lambda	253.43	5.71-26.30

Table 1 continued

Laboratory test	Value	Normal reference value
Kappa/lambda index	0.09	0.26–1.65

A monoclonal IgG lambda is found
Urine immunofixation: A monoclonal IgG component with no light chain is found, as well as a Bence-Jones lambda component

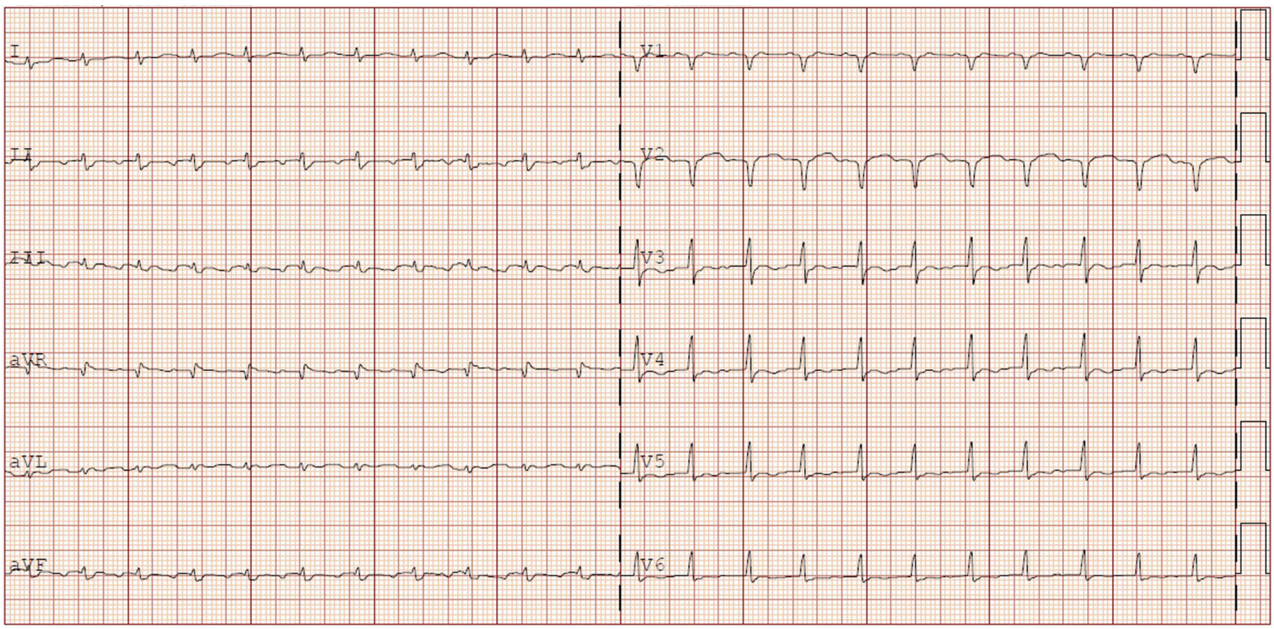

Figure 1. A 12-lead ECG performed at the emergency care admission, an atrial flutter and generalized low voltages are appreciated.

The formal diagnosis of cardiac amyloidosis requires an endomyocardial biopsy (EB) to assess the presence of amyloid protein and determine the amyloid fibril type, but many electrocardiographic and imaging techniques have been proposed and has proven to have good sensibility and specificity for clinically diagnosing and help differentiation between cardiac amyloid types without the need of histological confirmation.[5,6] Scintigraphy with Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-99m-DPD) has proven its high sensibility and specificity for differentiating ATTR amyloidosis from AL amyloidosis based on the Perugini visual score [6] and quantitative analysis comparing the heart-to-contralateral ratio.[7] This case presents a young patient diagnosed of AL amyloidosis even though he had a Perugini Grade 3 on Tc-99m-DPD scintigraphy.

CASE REPORT

A 40 years old male patient goes to the emergency department due to palpitations. The patient reports that the episodes of palpitations began 3 months previously, these being unrelated to the effort and self-limited. Occasionally, he had presented chest pain of atypical characteristics in the right hemithorax with the efforts.

The patient has no cardiovascular risk factors or past medical history, or takes any medication. Upon arrival at the emergency room, the patient's blood pressure is 100/70 mm Hg, 140 BPM, 100% $SatO_2$, and a temperature of 96.8 °F. At physical examination, no jugular engorgement, with tachycardic rhythmic sounds, without murmurs. At pulmonary auscultation, lungs well ventilated without added noises. The abdominal examination was normal, with mild bimalleolar edemas, without signs of deep vein thrombosis.

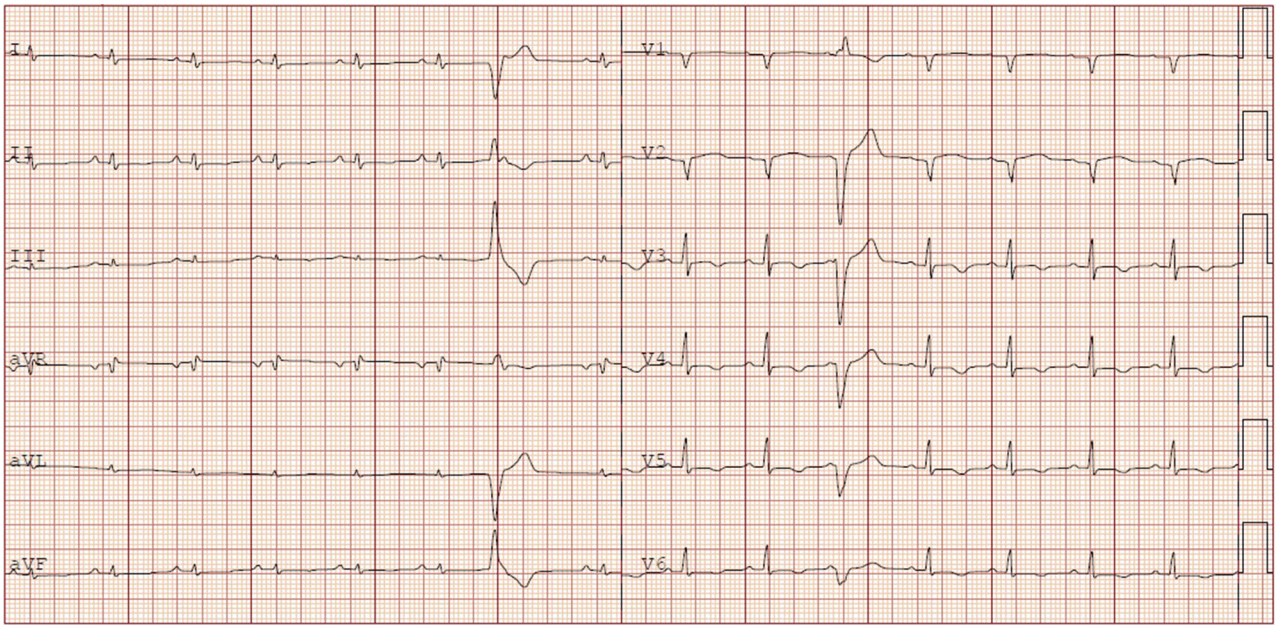

Figure 2. A 12- lead ECG after spontaneous cardioversion is shown, in sinus rhythm and persisting low voltages.

In the complementary tests performed, a complete blood count, biochemistry and coagulation is received, shown on Table 1. In the ECG at arrival to emergency room, a typical atrial flutter at 140 BPM, narrow QRS, normal axis, negative T waves in V3-V6 and low voltages on all leads were appreciated (Figure 1). The chest radiograph shows a normal cardiothoracic index, without masses, condensations, or congestive signs.

After administration of a single oral dose of Bisoprolol 2.5 mg, heart rate control is achieved and spontaneously reverted to sinus rhythm about 4 hours later, with persistence of low voltages and previously mentioned repolarization alterations in precordial leads (Figure 2). During inpatient, markers of myocardial damage remained elevated and on plateau, as also was serum creatinine, while the other routine laboratory tests were performed (Table 1).

An echocardiogram is performed, showing a left ventricle (LV) of normal size and thickness, with mild global hypokinesia, LVEF 46%. Transmitral flow pattern suggestive of restrictive pathology (with an E/A ratio of 2.9 and E/e´ of 15.7), shown on Figure 3. Slightly dilated RV with mild hypokinesia of the free wall, moderate functional mitral regurgitation and moderate tricuspid insufficiency with estimated PCAP of 33 mm Hg. The LV longitudinal STRAIN in three different axes showed a preserved apical function with a progressive hypokinesia through the base, with a typical bulls-eye pattern that is shown on Figure 4.

Into the differential diagnosis of restrictive cardiomyopathies, hemochromatosis is left aside due to iron deficiency, very low transferrin saturation index and normal serum ferritin and transferrin levels (Table 1). It is decided to perform a cardiac magnetic resonance imaging (CMRI) in which a normal-sized left ventricle can be seen, with 51% LVEF and mild septal hypertrophy (15 mm) with mild dilated left atria (LA), shown on Figure 5. Late Gadolinium Enhancement (LGE) is shown on Figure 6, where a diffuse subendocardial uptake in LV, right ventricle and both atria with difficulty for complete myocardial suppression is appreciated, findings suggestive of cardiac amyloidosis.

A Tc-99m-DPD planar scintigraphy is performed (Figure 7) in which diffuse myocardial deposition was obtained, with biventricular distribution and predominantly in LV, with greater uptake than the bone (Perugini visual score Grade 3) on a semiquantitative analysis (Figure 7A). For the quantitative analysis, a comparison between regions of interest (ROI) in the heart area and corrected for contralateral counts on the right hemithorax, a ratio of 1.67 is obtained (Figure 7B). These results were interpreted as compatible with cardiac amyloidosis by transthyretin, so a single-photon emission computed tomography was not performed.

Serum proteinogram was requested with normal alpha 1, alpha 2, beta and gamma fractions. A monoclonal peak in serum is found, so a kappa and lambda serum immunofixation is performed. In the

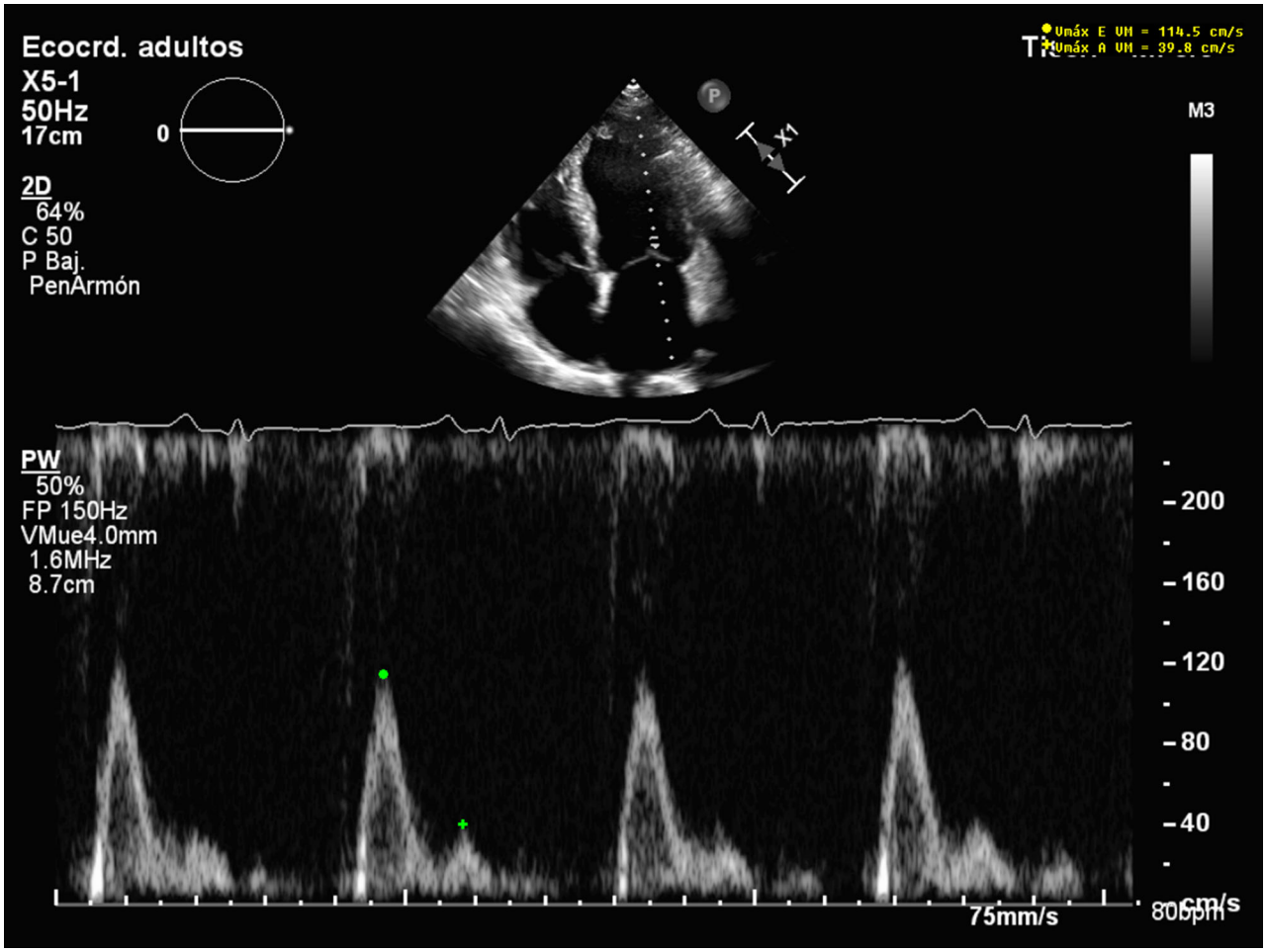

Figure 3. Pulsated doppler of transmitral flow. A maximum velocity of E wave of 114.5 cm/s and A wave of 39.8 cm/s for a ratio of E/A of 2.9 is show, typical of a restricted LV relaxation pattern.

immunofixation of urine, monoclonal component IgG without light chain and another Bence-Jones lambda was obtained (results can be found on Table 1).

Abdominal fat biopsy is requested and is analyzed using Congo red dye with a negative result. A bone marrow biopsy was performed which neither stains with Congo red dye and shows normal cellularity with infiltration of 7.75% of plasma cells (normal value $< 3.5\%$). No cytogenetic alterations in the fluorescence in situ hybridization (FISH) were found on the bone marrow cells. These results are suggestive of monoclonal gammopathy of uncertain significance. The sequence of the TTR gene was studied twice following the Sager method, ruling out mutations on any of its 4 exons.

Since the results of the Tc-99m-DPD scintigraphy were highly suggestive of ATTR amyloidosis but a monoclonal peak was found on serum, an EB was performed for histologic characterization, shown on Figure 8. Amyloid deposition between myocardiocytes that stains with Congo red dye was found, with positive Kappa and Lambda light chains on immunohistochemistry, being the AL cardiac amyloidosis the definitive diagnosis. The treatment plan was 6 cycles of 4 doses of bortezomib 2.7 mg and 3 doses of cyclophosphamide 650 mg but suffered sudden death at home during first cycle.

DISCUSSION

In this paper, we present a case of a young patient that had a new onset atrial flutter with low voltages on the ECG and a non-hypertrophic LV restrictive pattern on echocardiography pulsated doppler. It is known that almost one third of the cases of cardiac amyloidosis has a normal ventricular wall thickness,[8] so a CMRI was performed and the LGE pattern was suggestive of cardiac amyloidosis.

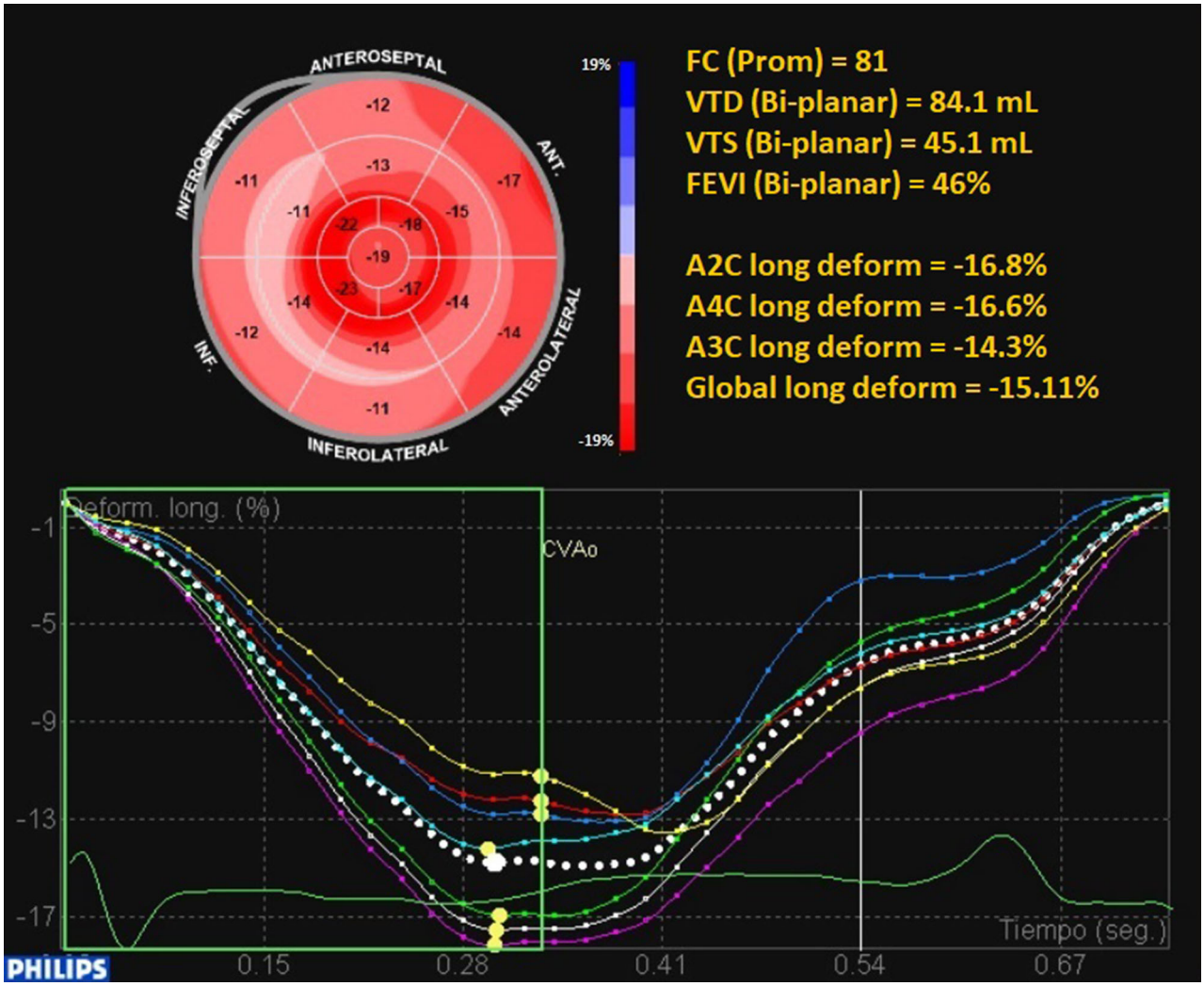

Figure 4. Bulls-eye pattern on the LV STRAIN technique. A normal apical function (less than − 19) is shown, with a progressive hypokinesia through the LV, most marked on the basal segments.

To assess the type of amyloidosis a Tc99m-DPD planar Scintigraphy was performed and a Perugini grade 3 with a ratio of 1.67 of heart-to-contralateral counts were obtained. Even though these result are strongly suggestive of cardiac amyloidosis by ATTR, and some studies have demonstrated that scintigraphy is an excellent tool for differentiating AL and ATTR cardiac amyloidosis,[6,7] we decided to perform an EB which was positive for AL amyloidosis.

Prior to this case, following the results of an original paper, of the complete study population only one patient with AL amyloidosis was reported with a Perugini visual score grade 3, but that patient had a previous myocardial infarction and a focal deposition (non-diffuse as it is typical on cardiac amyloidosis) and it was performed with another reactant, the Tc99m-PYP.[7] Visual score grade 2 is also very uncommon on AL amyloidosis.[6,7,9] The quantitative analysis using ROI to compare counts on the heart area versus counts on the contralateral hemithorax was also strongly suggestive of cardiac amyloidosis by ATTR as the ratio was greater than 1.5, following the results of previous studies (also performed with the Tc99m-PYP).[7] These findings suggest that despite the high sensibility and specificity of Tc99m-DPD scintigraphy, is recommendable to accept the scintigraphy limitations for differentiating AL and ATTR amyloidosis when a monoclonal protein is found, and perform an EB in this situation.

A consensus document proposes that all patients with a CMRI suggestive of cardiac amyloidosis should get a Tc99m-DPD/PYP/HMDP scintigraphy and rule out the presence of a monoclonal gammopathy, and only

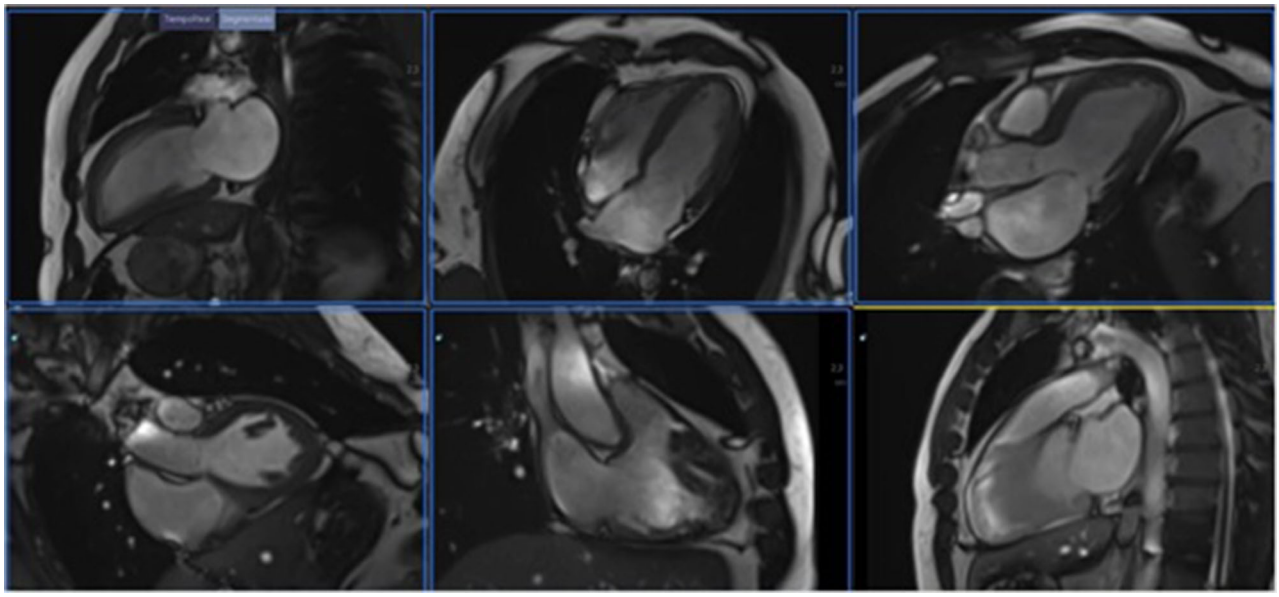

Figure 5. CMRI on long axis views. A normal size LV with 51% of LVEF and mild dilated LA can be appreciated.

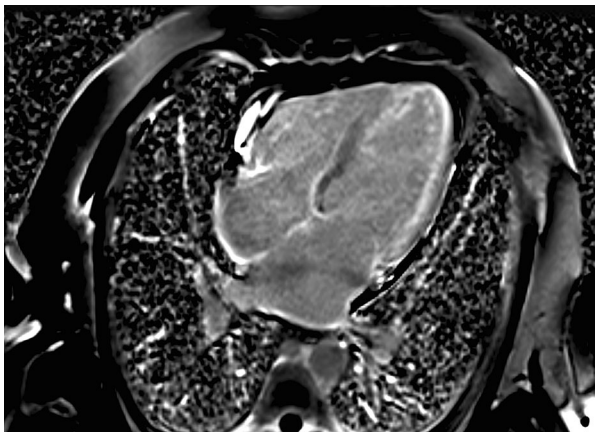

Figure 6. CMRI showing LGE with diffuse subendocardial uptake in VI, RV and both atria.

patients with Perugini grade 2 or 3 without a monoclonal serum protein could be diagnosed of ATTR cardiac amyloidosis without an EB. Patients with Perugini grade 2 or 3 with a monoclonal protein peak on serum or urine should get and EB for histological diagnosis.[10]

With the final diagnosis of this case, we show that in many cases even if we have scintigraphy strongly suggestive of ATTR cardiac amyloidosis, if a monoclonal peak on serum is found, EB should be performed for a histological confirmation. Having a histological confirmation allows to start a correct treatment and stop disease progression.

Disclosure

Yvan Persia, Javier Cuevas, Rodrigo Fernández, Alejandro Junco Vicente, Jose Rozado Castano, Santiago Colunga, Helena Cigarran, Juan Calvo, Alfredo Laverde, Osiris Persia and Esmeralda Capin as authors of this case report have nothing to declare.

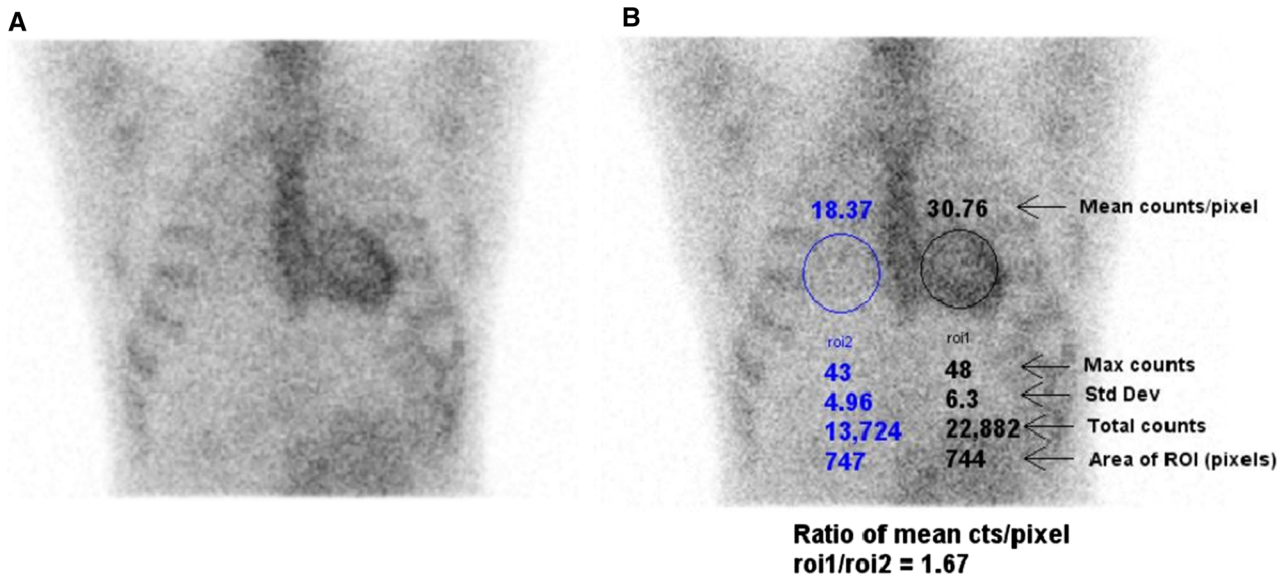

Figure 7. TC-99m-DPD planar scintigraphy showing a diffuse biventricular deposition most marked than bone (Perugini Grade 3) on semiquantitative assessment (**A**) and a quantitative analysis comparing the ROI in the heart area (roi1) corrected for contralateral counts (roi2), calculating the heart-to-contralateral ratio with a 1.67 as result (**B**).

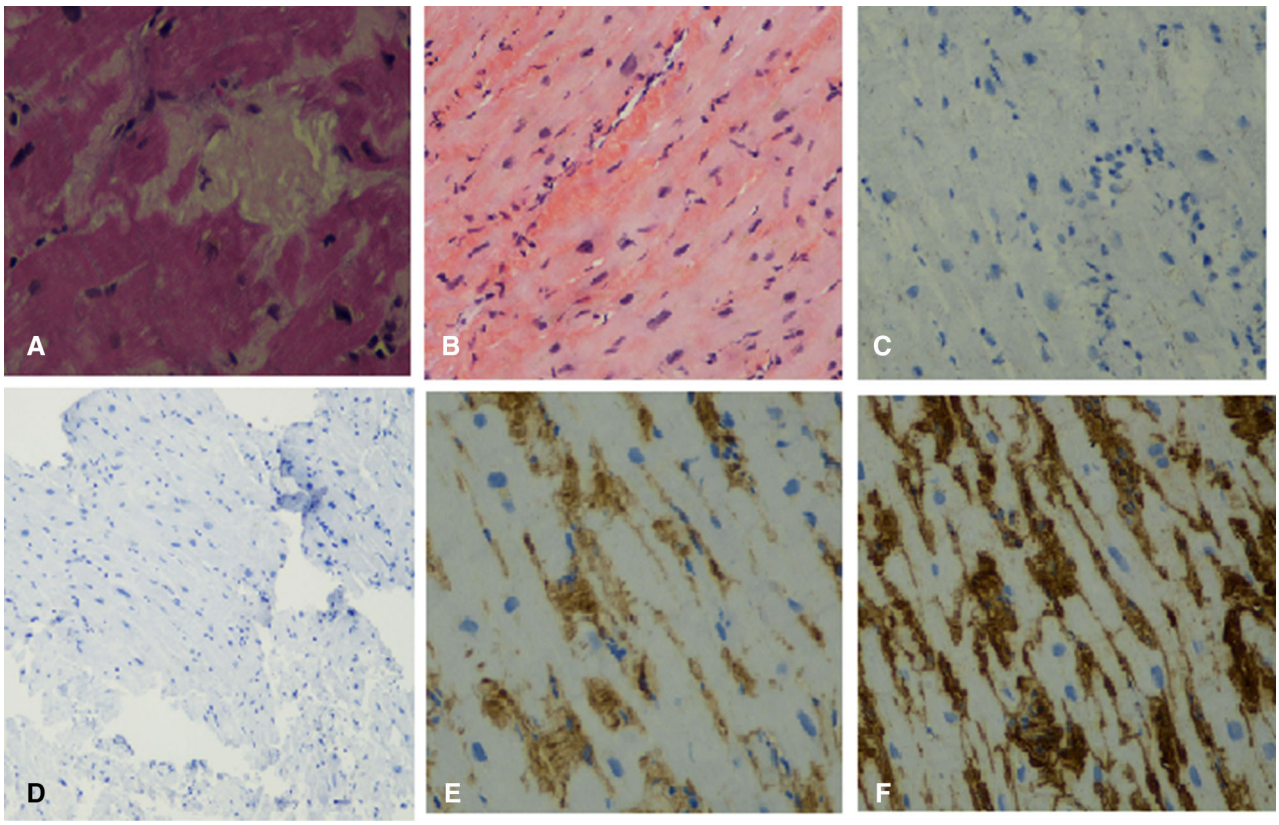

Figure 8. Endomyocardial biopsy. **A** Hyaline amorphous material between myocardiocytes. **B** Positive Congo red stain. **C** Immunohistochemistry for AA amyloid, negative result. **D** Immunohistochemistry for transthyretin amyloid, negative result. **E** Immunohistochemistry for kappa light chain, mild positive result. **F** Immunohistochemistry for lambda light chain, strongly positive result.

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