European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 26 – July 2010

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

please find enclosed the 26th issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the case resolution from the June case.

On the last page of the newsletter you will find some recommendations for further reading with a list a recently published papers in the field of our WG……

Best wishes for all of you.

S. Pankuweit

The paper of the month:

Multiple mutations in desmosomal proteins encoding genes in arrhythmogenic right ventricular cardiomyopathy/dysplasia


B. Bauce, A. Nava, G. Beffagna, C. Basso, A. Lorenzon, G. Smaniotto, M. De Bortoli, I. Rigato, E. Mazzotti, A. Steriotis, M. P. Marra, J. A. Towbin, G.Thiene, G. A. Danieli, A. Rampazzo, Heart Rhythm 2010;7:22–29

by Roberto Barriales-Villa and Lorenzo Monserrat. *Cardiology Service. Instituto de Investigación Biomédica A Coruña. A Coruña. Spain.*

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic cardiomyopathy characterized by fibrofatty replacement of right, and sometimes left, ventricular myocardium and electrical inestability associated with ventricular tachycardia. It is one of the commonest causes of sudden cardiac death in the young. Conversely, a benign course has been observed in many patients with ARVC/D suggesting a spectrum of clinical profiles and prognoses. The classic description of the disease presents the end stage of a process where the myocardium, mainly of the right ventricle, has been substituted by fibrofatty tissue. Thus the early stages of the disease with subtle morphologic signs and symptoms are often missed and its diagnosis is often a challenge for the clinician. Moreover, it has been described interfamilial and intrafamilial variability, ranging from benign to malignant forms with a high risk of sudden cardiac death. The mode of inheritance is mostly autosomal dominant with incomplete penetrance, but also recessive forms, like Carvajal syndrome a Naxos disease, have been described.

Over the past decade, the understanding of the disease has increased dramatically along with delination of the genetic basis and characteristic features on diagnostic imaging of ARVC/D. With the recent publication of a proposed modification of the Task Force criteria, a new frontier is open in the ARVC/D diagnosis.

SUMMARY OF THE ARTICLE

In this article a cohort of 42 consecutive index cases with a typical form of ARVC/D was investigated at the Department of Cardiothoracic and Vascular Sciences of the University of Padua, Italy. The study protocol included: physical examination, family history, 12-lead electrocardiogram (ECG), signal-averaged ECG, 24-hour Holter ECG and 2-dimensional echocardiogram. Diagnosis was made according to the past Task Force criteria. Moreover, family members of these 42 subjects were also analyzed using the same clinical protocol. The index case patients were screened for mutations in PKP2, DSP, DSG2, DSC2, JUP, and TGFβ3 genes by denaturing high-performance liquid chromatography (DHPLC) and direct sequencing. A control group of 250 healthy and unrelated subjects (500 alleles) from the Italian population was used to exclude that the detected mutations were DNA polymorphisms. Among these 42 unrelated ARVC/D index cases, 7 (16.6%) carried a PKP2 mutation, 5 (11.9%) a DSP mutation, 4 (9.5%) a DSG2 mutation, 2 (4.8%) a DSC2 mutation, and 2 (4.8%) a TGFβ3 mutation. No one carried JUP mutations. A potential disease causing mutation was found in 38% of the cases. Overall, 3 index cases (7.1%) carried multiple mutations in the same gene or in different genes. Family screening identified an additional 7 multiple-mutation carriers. Among the 7 double heterozygotes for mutations in different genes, 2 were clinically unaffected, 2 were affected, and 3 showed some clinical signs of ARVC/D even if they did not fulfill the diagnostic criteria.

Two compound heterozygotes for mutations in the same gene and 1 subject carrying 3 different mutations showed a severe form of the disease with heart failure onset at a young age. Moreover, multiple-mutation carriers showed a higher prevalence of left ventricular involvement (P=.025) than single-mutation carriers.

The authors conclude that the occurrence of compound and double heterozygotes in ARVC/D index cases is particularly relevant to mutation screening strategy and to genetic counseling. Even if multiple-mutation carriers show a wide variability in clinical expression, the extent of the disease is higher compared to that in single-mutation carriers.

COMMENTARY

Critical review of the article suggests us to focus our attention on three important aspects:

1. Multiple mutations in the same gene or in different genes in ARVC/D. The presence of multiple mutations has been found to occur in either the same gene (compound heterozygotes) or in different genes (double heterozygotes) in different inherited cardiomyopathies. Thus in HCM multiple mutation carriers account approximately up to 5%. It is known that individuals who carry 2 disease-causing familial HCM mutations have a more severe disease than patients with single mutations, including earlier onset, more severe left ventricular hypertrophy and heart failure and a higher rate of sudden death events (resuscitated cardiac arrest or sudden death). Recently an article by Girolami et al described a more complex genotype (triple sarcomeric mutations) in a cohort of patients with HCM, showing an increased risk of end-stage progression and ventricular arrhythmias in these patients, supporting an association between multiple sarcomere defects and adverse outcome.

Identification of complex genotypes when studying inherited cardiomyopathies is not uncommon, and probably it's becoming evident with the widespread use of genetic studies. It sounds plausible that the more complex genotype, the more complex phenotype would be expected, but it cannot be considered as a general rule. A highly malignant mutation may have a more severe phenotype than the presence of a combination of less severe variants.

2. Genetic study methodology in ARVC/D. On the basis of the reported findings, genetic screening of desmosomal ARVC/D genes should not be stopped after the identification of one mutation in one gene and should be continued at least on the main desmosomal ARVC/D genes (PKP2, DSP, DCS-2 and DSG-2). Probably this genotyping strategy should include other genes as TMEM 43 that have been related with the disease.

3. New ARVC/D diagnostic criteria. With the proposed modification of the Task Force, genetic studies have come to represent a major criterion in the diagnosis of the disease. Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation is considered to be a major criterion on ARVC/D diagnosis. The new Task Force consider a pathogenic mutation a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

But this is not as simple as it sounds. It is often difficult to establish whether a mutation is pathogenic or not. There are several limitations:

- functional studies are usually not conclusive,
- the number of ethnically matched controls is usually small,
- there are multiple problems to establish the cosegregation of the genetic variant in the family, including incomplete penetrance and the presence of double mutations in the same family.

It's therefore essential to obtain information about the clinical and genetic data of all the genetic variants. It's very important to publish articles like this of Bauce et al, which provide clinical, genetical and complete family studies of ARVC/D. We know that in medicine no single test is able to provide a definite diagnosis in any disease. In inherited cardiomyopathies a correct diagnosis requires the integration of clinical, morphological and familial studies, together with the genetic tests.

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The clinical case of the month: *What is your diagnosis?*

Answers will be given in the next newsletter and on the web site

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Confounding presentation phenotype in familial cardiomyopathy

Proband history

The proband is a 42-year-old male diagnosed with idiopathic dilated cardiomyopathy few years ago and followed-up in another Centre. Clinical reports of the 1st evaluation were unavailable.
In March 2009 the coronary angiography documented absence of significant stenoses. He underwent ICD implantation on March 6th, 2009.

In April 2009 he had an episode of acute heart failure as result of therapy discontinuation on his own. He mentioned he had dyspnoea on mild efforts, orthopnoea and gain of weight. The echocardiogram showed severely depressed left ventricular systolic function (EF 15%). An increased and dishomogeneous echo-reflectance of the myocardium suggested the hypothesis of infiltrative cardiomyopathy. Peri-umbilical fat biopsy was described as positive for amyloid. The sample was untreacble.

The patient came to our attention at the end of July, 2009; the diagnostic suspect was cardiac amyloidosis; alternatively, storage disease (i.e. Anderson-Fabry Disease).
July 31st, 2009:

- Electrocardiography (figure 1): incomplete right bundle branch block, ST abnormalities (↑ in inferior leads) and repolarization abnormalities (negative T waves in inferior leads and in C4-C6);

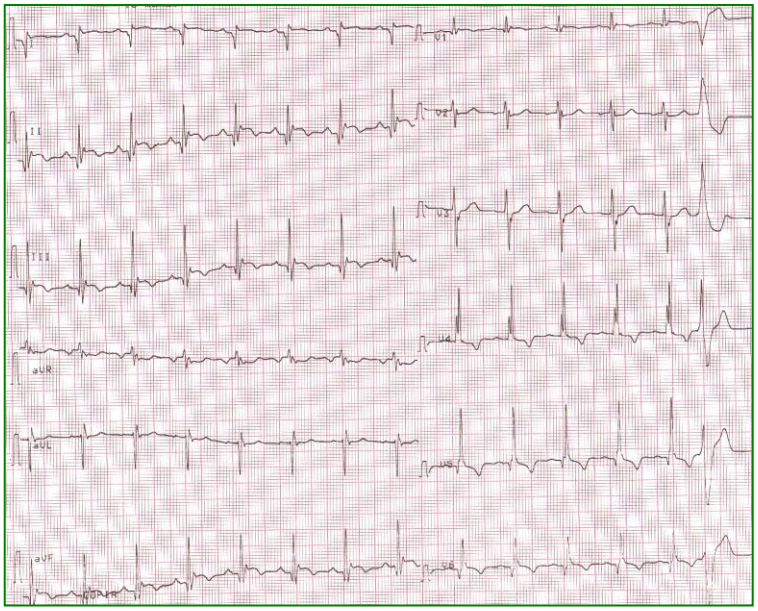

Figure 1.
ECG of the proband. Diffuse ST-T abnormalities with ↑ST in the peripheral inferior leads and negative T waves in inferior leads and precordial C4 to C6. Isolated ventricular ectopic beat. ECG voltage criteria for left ventricular hypertrophy (Sokolow-Lyon).

Echocardiography (figure 2): left ventricular dilation (LV end-diastolic diameter 72 mm, LV end-diastolic volume 262 ml) with severe impairment of systolic function (EF 15-20%), interventricular septum thickness 10 mm (basal segment) and of irregular echo-reflectance of the myocardium and diffuse hypokinesis. Moderate-to-severe mitral regurgitation due to leaflet tethering;

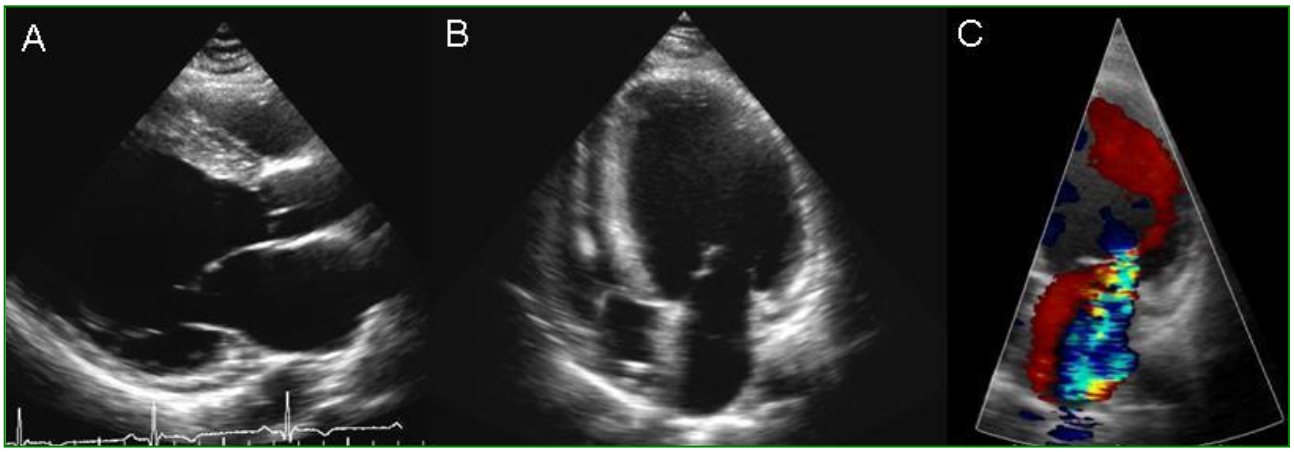

Figure 2. Echocardiogram of the proband. (A) Parasternal short axis view: left ventricle dilation, irregular echo-reflectance of the septum, thinning of the posterior wall, mild left atrium dilation. (B) apical four-chamber view: left ventricular dilation, normal right ventricle; in the right ventricle evidence of the catheter of the ICD. (C) Color-Doppler from the apical four-chamber view showing the mitral regurgitation.

- Right Cardiac catheterization: mild-to-moderate pulmonary hypertension (systolic pulmonary arterial pressure 38 mmHg), mild increase of wedge pressure (10 mmHg);
- Endomyocardial biopsy: focal myofibrillolysis, myocyte disarray, interstitial fibrosis. Absence of inflammation, thrombosis and interstitial deposits.
- Biochemistry:

	Result:	**Normal range:**
- B-type Natriuretic Peptide	424 pg/ml	0-50
- Total CPK	197 mU/ml	24-190
- CK-MB	35 mU/ml	5-24
- Troponin I	2.155 ng/ml	0-0.04

The patient gave his informed consent to genetic and molecular analysis and a blood sample was collected with this scope.
Drug therapy with diuretics, beta-blocker and ACE-inhibitor was progressively up-titrated and the patient improved gradually till functional NYHA class II. BNP mildly diminished to about 200 pg/ml. Ejection fraction of the left ventricle improved up to 35%.

Questions:

1) **Do you agree with the diagnosis of idiopathic dilated cardiomyopathy vs the original diagnosis of infiltrative disease?**
2) **Would you suggest further biochemical examination or instrumental evaluations?**

The family screening only included a younger brother who came to our attention on December 18th, 2009. He described an atypical episode of chest pain in 2001 for which he was admitted to the Emergency Department. The clinical report was not available. According to the description, the biochemical analyses were negative, the ECH showed incomplete right bundle branch block and no signs of myocardial ischemia. He was said that the his heart showed "initial dilation".

A Cardiac MRI was performed October 1st, 2009 and showed left ventricle with evidence of severe asymmetrical hypertrophy with maximum thickness ***21 mm*** in the septum; dilation of the left ventricle and diffuse hypokinesis. Small areas of hyper-enhancement in the interventricular septum and anterior basal wall of the left ventricle. Delayed enhancement from endo- to epicardium in the inferior and lateral wall and in the interventricular septum (basal and medium segments). The conclusion indicated the possibility of a infiltrative cardiomyopathy.

At our centre, he underwent:

- Electrocardiography (figure 3): deep and large (>40 msec) Q waves in inferior leads; diffuse repolarization abnormalities with negative T waves in DIII and in C4-C5;

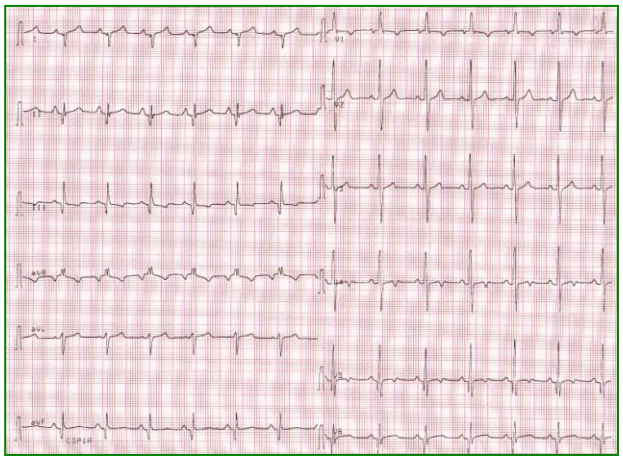

Figure 3.
Electrocardiogram of proband's brother. Evidence of Q waves in inferior leads and repolarization abnormalities both in peripheral and precordial leads.

Echocardiography (figure 4): enlarged left ventricle (end-diastolic diameter 70 mm, end diastolic volume 209 ml); ***asymmetric*** left ventricular hypertrophy: septal thickness ***15 mm***, corresponding to a z score (according to Henry's formula based on age and BSA) of 5.6 (normal z score ranges from -2 to +2); thinning of posterior wall. Reduced left ventricular systolic function (***EF 30%***). Hypertrabeculation non fulfilling the criteria for left ventricular non-compaction. Mild mitral regurgitation due to leaflet tethering;

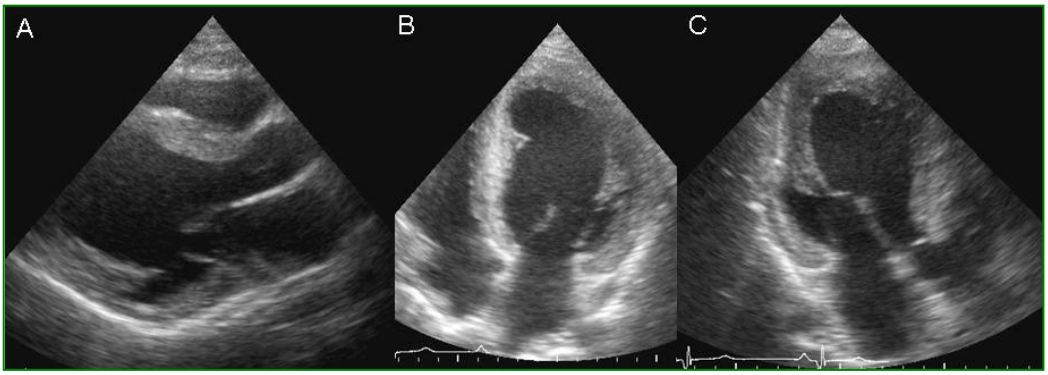

Figure 4.
Echocardiographic examination of proband's brother. (A) Parasternal short axis view. (B) apical four chamber view. (C) Apical three chamber view. Worth of notice the thinning of the posterior wall just at the basis of the papillar muscle.

- Biochemistry:

	Result:	Normal range:
- B-type Natriuretic Peptide	87 pg/ml	0-50
- Total CPK	306 mU/ml	24-190
- CK-MB	39 mU/ml	5-24
- Troponin I	0.224 ng/ml	0-0.04

- Endomyocardial biopsy (January 10th, 2010): hypertrophic myocytes and presence of focal interstitial fibrosis; presence of rare and focal optically empty myocytes. Normal expression of Dystrophin. Ultrastructural study documented the absence of amyloid and of intra-myocyte osmiophilic deposits that could be consistent with the diagnosis of AFD.

The patient was given beta-blockers, ACE-inhibitors and low doses of furosemide and spironolactone. He reported mild improvement in the subsequent weeks.

Questions:

3) **Would you change the diagnostic hypothesis of familial DCM on the basis of the additional information coming from the proband's brother?**
4) **Considering the peculiar evidence on the endomyocardial biopsy of the proband's brother, which gene would you screen in the two brothers?**

Answer for the previous" Clinical case of the month" presented in June

"Sudden Cardiac Death Ten Months After Delivery"

by Arthur Pollak MD[1], Dan Admon MD[1], Dina Ben-Yehuda MD[2], Andre Keren MD[1] from the Division of Cardiology[1] and the Department of Hematology[2], Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Diagnosis, case resolution and treatment

Sudden cardiac death (SCD) in a middle aged woman, 10 months after delivery, requires consideration of several possible diagnoses. The lack of a history of SCD in the family as well as the normal QT interval and absence of Brugada pattern on the presenting ECG (figure 1) make congenital long QT or Brugada syndrome very unlikely. This is further supported by the negative procainamide challenge test and by the fact that the patient was not receiving any medications to influence the conduction system or cause electrolyte imbalance. An acute ischemic event or underlying "silent" coronary disease should be considered next. Although a woman of young age, she had hyperlipidemia, a family history of coronary disease and symptoms which could reflect equivalent angina. Furthermore, the ECG (fig 1) was suggestive of an old anterior infarction (not supported by the normal left ventricular segmental wall motion and systolic function on echocardiography).

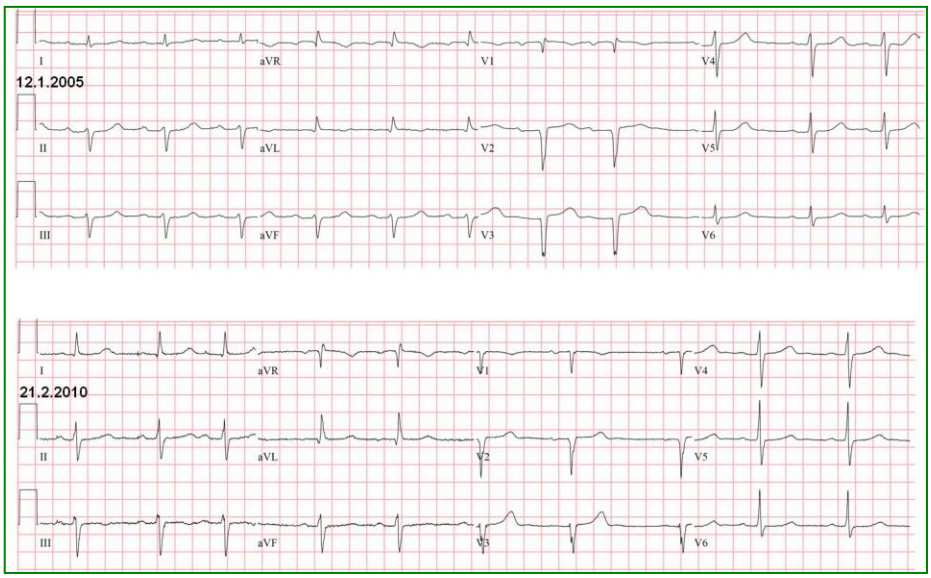

Figure 3: Two electrocardiograms recorded 5 years apart. There is a two- to three-fold increase in QRS amplitude, shorter PR interval and a lesser degree of left axis deviation. Poor R-wave progression in V1-V3 ("pseudo-infarction" pattern) is unchanged.

Thus, a coronary angiogram was performed and ruled out this diagnosis. Undiagnosed idiopathic dilated cardiomyopathy (DCM) or peripartum cardiomyopathy (PPCM) were not supported by the echocardiograms showing normal left ventricular (LV) size and systolic function. Myocarditis, in particular of giant cell type, may present as SCD due to malignant ventricular arrhythmias. However, the patient did not experience upper respiratory or gastrointestinal symptoms, nor did she have fever, to suggest a preceding acute viral infection. The lack of inflammatory markers (i.e. normal CRP) and the normal wall motion and systolic function further diminish the likelihood of this diagnosis. Modestly elevated CPK may reflect an acute myocardial injury, ischemic or inflammatory, but in her case could also be due to the delivery of electrical shocks during resuscitation (troponin measurement was not available at that time). A myocardial biopsy to rule out acute myocarditis or inflammatory cardiomyopathy could have been considered, but was not performed due to the low likelihood of these diagnoses.

Other forms of cardiomyopathy, hypertrophic and restrictive, may predispose to SCD in the middle age. The echocardiogram (figure 2) shows concentric biventricular wall thickening and biatrial enlargement. Doppler mitral flow-velocities are consistent with a restrictive filling pattern (E/A ratio = 3.7), suggestive of elevated LV diastolic pressure, in accordance with the measured LVEDP on heart catheterization.

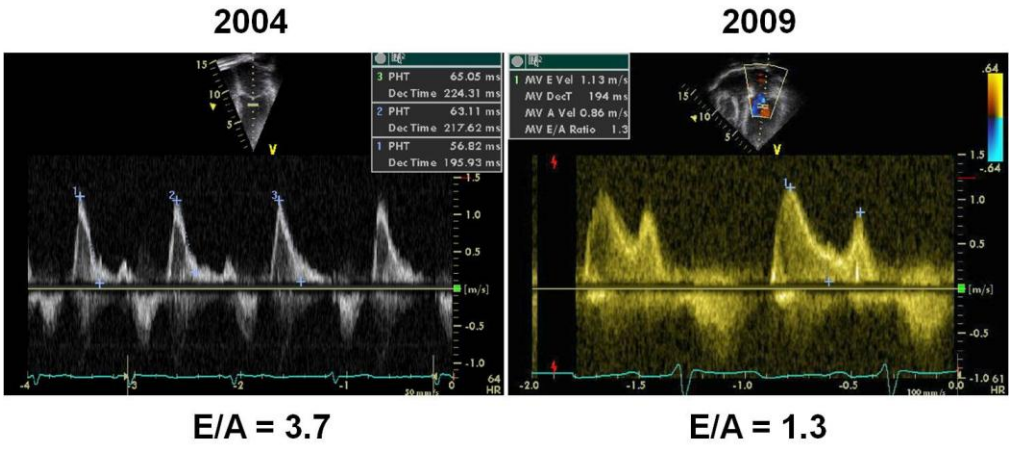

Figure 4: LV inflow Doppler tracings taken 5 years apart. The restrictive E/A pattern evident on the left has normalized on the right. However, mitral annular velocities are low (E' = 5.5 cm/sec), suggesting significantly impaired myocardial relaxation (tracing not shown). Note: heart rate is similar on both tracings, 61-64 /min, despite different recording speeds

These findings may support either restrictive or hypertrophic cardiomyopathy (HCM). However, the ECG, showing an anterior pseudo-infarction pattern and no left ventricular hypertrophy, does not support the diagnosis of HCM. On the contrary, the combination of a relatively small QRS voltage in the limb leads with conduction disturbances (left axis deviation and prolonged PR interval), and the aforementioned pseudo-infarction pattern, pointed to *restrictive amyloid cardiomyopathy* as the likely diagnosis. Signs and symptoms of congestive heart failure, often with right-sided predominance, are common in ***cardiac amyloidosis (CA)*** and may progress rapidly (1-3). LVEDP, mean right atrial and mean pulmonary wedge pressures are elevated in up to 2/3 of patients with CA (1,4,5). In addition, carpal tunnel syndrome is present in 13-38% of patients with CA and may precede other organ involvement by a few years (1,4).

The preliminary diagnosis of CA in our patient was supported by abdominal fat-pad, rectal and bone marrow biopsies showing positive Congo red amyloid staining. Assessment of serum and urine free light chains revealed excess of free kappa chains with an abnormally elevated kappa-to-lambda ratio. Bone marrow plasma cell count was about 10% (elevated but not diagnostic of multiple myeloma), and immunoperoxidase staining was positive for kappa-producing plasma cells. Thus, the diagnosis of systemic AL amyloidosis with cardiac involvement was made.
The management of AL amyloid cardiomyopathy requires both control of cardiac-related symptoms and treatment of the underlying plasma cell dyscrasia. Heart failure symptoms are best managed by diuretics and modest salt restriction, while angiotensin converting enzyme inhibitors and angiotensin receptor blockers are poorly tolerated in these patients. The use of beta blockers is often limited due to hypotension and conduction abnormalities, and no data exist to suggest any survival benefit from beta blockers in CA. Calcium channel blockers are contraindicated as they significantly worsen heart failure because of their negative inotropic effect. Cautious use of digoxin may be considered for heart rate control in patients with atrial fibrillation, although the risk of cardio-toxicity is increased due to avid binding of this drug to amyloid fibrils (1,3).

Treatment of AL amyloidosis requires anti-plasma cell therapy aimed at stopping, or significantly reducing, the production of amyloidogenic monoclonal light chains. Several chemotherapeutic regimens exist, including high-dose melphalan with autologous stem cell transplantation, standard dose melphalan with dexamethasone, and newer protocols incorporation thalidomide, lenalidomide and bortezomib, with or without steroids. Although controversial, heart transplantation followed by autologous stem cell transplantation may be considered in selected patients (3).

Our patient was initially treated with high dose melphalan and autologous bone marrow transplantation. Partial relapse of her disease was noted one year later. She was started on thalidomide but had only modest response. Due to inadequate control of disease and despite the increased risk, she underwent repeat stem cell transplantation. She currently receives lenalidomide as maintenance therapy. With time, her functional capacity markedly improved to NYHA class IIa. There was no recurrence of complex ventricular arrhythmias and no ICD discharge. At present, 6 years after diagnosis, she is active and working, with no signs of heart failure. She does not require diuretic therapy and does not receive antiarrhythmics. Reversal of ECG pathology and echo-Doppler findings has been noted on serial examinations (figures 3 and 4) and is consistent with her good clinical condition.

Comments on special aspects of the case

1. Delay in diagnosis

CA is frequently overlooked at initial presentation. In a recent report of 30 patients with CA (83% AL type) the time to diagnosis after initial presentation with clinical and/or ECG signs was 6 months to 4 years (2). In another series, 45% of patients had a delay in diagnosis of over a year from the onset of symptoms (6). Patients were misdiagnosed as having hypertrophic cardiomyopathy, heart failure of uncertain etiology or constrictive pericarditis. The delay in diagnosis is due to unrecognized ECG and echocardiographic features of the disease, in particular the discrepancy between ECG voltage and echocardiographic ventricular wall thickness is overlooked. Thus, diagnosing CA requires a high index of suspicion, primarily in patients presenting with rapidly progressive dyspnea and peripheral edema of unknown origin, in conjunction with non-dilated ventricles and poor R-wave progression (2-4).

2. Sudden death as presenting symptom of CA and the role of ICD

About half of the patients with systemic AL amyloidosis have cardiac involvement (1,7). Nevertheless, ventricular tachyarrhythmias are an uncommon presenting feature (7-10). The reported incidence of SCD in those with CA is about 30% and most cases are due to electromechanical dissociation (EMD), atrioventricular block or asystole (11-12). Therefore, the protective role of ICD in CA is uncertain. Kristen et al. (9) implanted defibrillators in 19 patients with CA and syncope and/or high-grade ventricular premature beats or non-sustained VT. After a mean follow-up of 2.5 years, only 2 patients (10%) received shocks for sustained VT while 6 patients (32%) died of EMD (including one of the 2 patients who initially received a successful ICD intervention). Hess et al. (7) described 4 patients with CA who had out of hospital cardiac arrest, one of whom had VF as the presenting symptom of the disease, as documented in our patient. Up to nine consecutive shocks were needed to control recurrent VF and shocks often resulted in EMD or asystole, as was the case in our patient. The authors emphasized that CPR in CA is of limited effectiveness and carries a very poor prognosis (3 of the 4 patients died shortly after CPR, 2 of them in EMD). Finally, defibrillation thresholds may be elevated in patients with advanced CA, rendering ICD ineffective when repeat shocks for recurrent and persistent VF at

high energy are needed (7, 9,10). Thus, ICD placement in AL amyloidosis should be limited to patients with documented malignant arrhythmias (3).

3. Prognosis

Cardiac involvement in AL amyloidosis is associated with poor prognosis. The median survival of untreated patients with CA is 9-12 months in the absence of heart failure and 4-6 month in those with symptomatic heart failure at diagnosis (3,13). Aggressive chemotherapy with stem cell transplantation induces complete hematologic remission in 40% of cases and improves overall prognosis in patients with CA, if it is initiated early in the course of the disease (3,9). Unfortunately, this regimen carries up to 30% risk of peritreatment mortality in patients with advanced cardiac involvement and is contraindicated in patients with a LVEF < 40% and NYHA class III heart failure (1). At diagnosis, our patient had ECG and echocardiographic evidence of significant amyloid infiltration of the heart. Nevertheless, her young age and preserved systolic function enabled her to undergo bone marrow transplantation (twice) and although not in complete remission, she is alive and almost free of symptoms 6 years after her dramatic presentation.

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List of recently published papers in the field of our WG recommended for further reading:

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