Diagnosis of cardiomyopathies: tips and tricks for internists and general practitioners

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Abstract

Cardiomyopathies are little known to internists and general practitioners (GPs), and not always able to arouse the interest of cardiologists. Probably, this happens because cardiomyopathies are perceived as rare and complex disorders, a prerogative of a few dedicated centers. This may partly explain why the diagnosis of cardiomyopathy is often missed and, consequently, why cardiomyopathies are largely underdiagnosed. Internists and general practitioners should have an interest in these conditions, because cardiomyopathies are not as rare as generally perceived, and because their complexity can be unravelled with knowledge and methodology. Cardiomyopathies are defined as myocardial disorders in which the heart is structurally and functionally abnormal in the absence of coronary artery disease or abnormal loading conditions. Irrespective of the cardiac imaging technique used, a limited number of phenotypes are defined based on ventricular morphology and function. These basic phenotypes include hypertrophic (HCM), dilated (DCM), restrictive (RCM) and right ventricular (RVC) cardiomyopathies. The diagnostic work-up starts at this point and the main challenge is shifting from a descriptive level to an aetiological one.

Aim of this article is to describe a simplified approach that may help the non-specialist in the detection of the underlying causes of specific phenotypes, or at least may arise the diagnostic suspicion of cardiomyopathies in their everyday practice, referencing consequently the patients to specialised centres. We will focus our attention on the basic phenotypes, presenting a diagnostic work-up and a clinical case example for each of them.

The overall prevalence of all cardiomyopathies is estimated at least 3% in the general population. Nonetheless, some entities of this broad spectrum are largely underdiagnosed. Indeed, the new estimated prevalence of HCM is about 1:200 and, thus, the chance of meeting an affected patient in the everyday practice is higher than commonly thought.

The chance of diagnosing a cardiomyopathy increase if the clinician has acquired a so-called cardiomyopathy-specific mindset: the attitude to interpret the clinical, laboratory and instrumental findings in the context of a phenotypically defined cardiomyopathy.

The diagnostic pathway starts with a basic diagnostic approach that relies on simple tools, easily performable in any clinic: family history, physical examination, electrocardiogram and echocardiogram. This phase is crucial: the presence of clinically and instrumentally derived findings, commonly known as diagnostic red flags, may suggest a specific cause for a defined phenotype or may restrict our attention to a narrower spectrum of conditions. The approach to all patients should be multidisciplinary in nature, and the following steps of the work-up need a stepwise selection of appropriate diagnostic techniques. It also represents an iterative process in which the findings are acquired and the case constantly revalued in light of new information in order to identify a specific cause or let other differential diagnosis emerge.

Introduction

Cardiomyopathies are little known to internists and general practitioners (GPs), and not always able to arouse the interest of cardiologists themselves. Probably, this happens because they are perceived as rare and complex disorders, a prerogative of highly specialised centres. This may partly explain why their diagnosis is often missed and, consequently, why they are considered largely underdiagnosed.

Cardiomyopathies are defined as myocardial disorders in which the heart is structurally and functionally abnormal in absence of coronary artery disease (CAD) or abnormal loading conditions. Irrespective of the cardiac imaging technique used, a limited number of phenotypes are defined based on ventricular morphology and function. These basic phenotypes include hypertrophic (HCM), dilated (DCM), restrictive (RCM) and right ventricular (RVC) cardiomyopathies. The diagnostic work-up starts at this point and the main challenge is shifting from a descriptive level to an aetiological one.

Aim of this article is to describe a simplified approach that may help the non-specialist in the detection of the underlying causes of specific phenotypes, or at least may arise the diagnostic suspicion of cardiomyopathies in their everyday practice, referencing consequently the patients to specialised centres. We will focus our attention on the basic phenotypes, presenting a diagnostic work-up and a clinical case example for each of them.

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Hypertrophic phenotype

The HCM is defined by the presence of increased left ventricular wall thickness that is not solely explained by abnormal loading conditions. It represents the most common cardiomyopathy and its diagnosis is based on quantitative criteria, derived by the morphological evaluation of the left ventricle by cardiovascular imaging techniques, primarily the echocardiogram.

In HCM few sarcomere gene mutations represent the majority of cases, while other genetic and non-genetic causes account only for the 5-10%. In about a quarter of cases the aetiology remains unknown. The basic approach helps to exclude the most common causes of left ventricular hypertrophy (LVH) due to abnormal loading conditions (longstanding hypertension, valve diseases, congenital disorders, athlete’s heart) and, at the same time, allows collecting features suggestive of a specific cause. Other diagnostic clues can be collected with further specialised tests and multidisciplinary consultations. If this diagnostic process does not bring to a specific diagnosis, genetic test is than recommended. If a specific cause does not emerge even after genetic testing, all diagnostic clues should be reassessed, new and different diagnostic techniques considered and a multidisciplinary team meeting organized. Despite all efforts, in the 25% of cases it is not possible to recognize a definitive cause of HCM.

The family history can be useful in distinguishing between genetic and non-genetic causes. A significant family history of HCM, premature sudden cardiac deaths,
unexplained heart failure, pacemaker/defibrillator implantation, cardiac transplantation and other organ system involvement, all suggest a possible genetic cause. The pedigree analysis helps us to recognize the pattern of inheritance. Most of the genetic forms of HCM display autosomal dominant inheritance.15,16 On the other hand, autosomal recessive inheritance is less common and is typical in Friedreich ataxia and some mitochondrialopathies.17 The X-linked inheritance is the typical pattern of uncommon conditions such as Fabry and Danon disease.18 The matrilineal pattern of inheritance is a specific clue of mitochondrialopathies caused by mitochondrial DNA mutation.19 The age is a potential diagnostic clue: the presence of HCM in neonates and children suggests a congenital syndrome or an inherited metabolic disorder;20 genetic forms due to sarcomeric gene mutations are most common in young adults but can occur in any age of life;21 Danon disease occurs commonly in the first decades of life,22 while senile amyloidosis occurs primarily in the elderly.23 The symptoms in patients with HCM are non-specific and the physical examination is nearly normal in patients without an obstructive. In these last some typical features are present: a rapid upstroke and downstroke to the arterial pulse; an ejection systolic murmur due to LVOT obstruction (LVOTO) or to systolic anterior movement of the mitral valve (SAM).23

Other non-cardiovascular signs and symptoms that may suggest a specific cause of HCM are (Table 1): dysmorphic face in genetic syndrome such as Danon disease;23,24 visual impairment in mitochondrialopathies;23,28 palpebral ptosis in mitochondrialopathies and myotonic dystrophy;23,28 sensorineural deafness in mitochondrialopathies and Fabry disease;23,28,29 angiodermatoma in Fabry;29 sensory abnormality and bilateral carpal tunnel syndrome in amyloidosis.3

The electrocardiogram is typically abnormal in patients with HCM and is often the earliest manifestation, warranting further diagnostic evaluation and having a prognostic role.30,31 Some ECG patterns in presence of LVH may suggest a specific cause of HCM (Table 1): giant T-wave inversion on inferolateral leads in apical HCM;23 low voltage pattern with pseudo-infarct pattern in forms of amyloidosis other than TTR-amyloidosis;33,34 extreme high voltage pattern in storage diseases such as Danon and Pompe disease;23 short PR, with pre-excitation in many storage and mitochondrial diseases35,36 or alone in Fabry disease.29

The echocardiogram sometimes may suggest a specific diagnosis (Table 1): a ground-glass appearance of myocardium, in presence of thickened interatrial septum and/or atriocentric valves and/or of mild pericardial effusion, is the typical aspect of amyloidosis.39–41 a biventricular hypertrophy with thickened atriocentric valves, is suggestive of Fabry disease.42–44

The first-level laboratory tests performed in HCM are listed in Table 1 and may contribute to the diagnosis.

Other diagnostic tools, such as cardiac magnetic resonance (CMR), nuclear scintigraphy, genetic testing and endomyocardial biopsy, remain useful in diagnosis clarification and prognostic assessment, but for their costs, diffusion and invasiveness are still considered as second level techniques, their adoption in Internal Medicine Departments still being very limited.

First clinical scenario

A 74-year-old woman was admitted in our hospital because of recurrent episodes of chest pain. She had previously been admitted at the local Cardiology Department for the same reason, when a coronary angiogram showed normal epicardial coronaries.

The basic approach evidenced: a personal history diabetes mellitus and hypercholesterolemia, without hypertension, and a family history of CAD; an unremarkable physical examination; mild kidney failure due to LV failure; mild pericardial effusion, ground-glass appearance of myocardium, and low-normal systolic function (Figure 1B).

Anyway, showed normal LV size cavity with concentric hypertrophy, an isoechic apical formation with concomitant wall motion abnormality, and low-normal systolic function (Figure 1B).

The presence of an apical mass with concomitant wall motion abnormalities prompted the following differential diagnosis: apical thrombus, apical tumour, isolated apical obliteration due to endomyocardial fibrosis.45,46

The unremarkable recent coronary angiogram performed seemed to exclude a CAD. To better characterize the apical region a CMR was proposed but declined by the patient because of claustrophobia. Contrast echocardiogram was than performed using lung-penetrating agent and revealed hyper trophy of the apex with maximum apical wall thickness of 17 mm (Figure 1C). The ECG pattern was than the only red flag: the presence of giant T waves inversion in precordial and lateral leads, as described above, is indeed typical in apical forms of HCM.

Genetic testing was performed and revealed MYBPC3 gene mutation.

We concluded for apical hypertrophic cardiomyopathy due to sarcomere gene mutation with severe recurrent episodes of chest pain, which respond to beta-blocker.

Dilated phenotype

In DCM we should deal with a much complex phenotype, also at descriptive level.48 The most common causes of LV dilatation and dysfunction are CAD and abnormal loading conditions (longstanding hypertension, valve diseases, congenital disorders).49 When these are excluded, usually with a coronary angiogram and a cardiovascular imaging technique, less common causes should be considered. The information obtained by the basic approach can guide the physician in distinguishing between genetic and non-genetic causes (myocarditis, toxic damage from heavy metals, infiltrative disorders and metabolic derangements), and in planning subsequent work-up.

About the history taking, the most common questions concern the duration of disease, the rate of progression, the presence of antecedent illness, a history of recent travels, the presence of abnormal loading conditions, the use of drugs, alcohol or the exposition to other toxins and the presence of coronary risk factors.50 In order to understand if we are dealing with a genetic cause, a family tree should be drawn and a pedigree analysis performed. Nonetheless, a not significant genetic tree does not exclude a genetic cause of DCM because of the low penetrance of many genetic mutations.51

A history of premature atrial fibrillation, conduction diseases, pacemaker and/or defibrillator implantation suggests the presence of genetic causes such as laminopathies, desminopathies and some dystrophinopathies.52,53 In this case the pattern of inheritance could be helpful.54 Many genetic causes have also manifestations in other organ systems: for example, a familial history of neuromuscular disease and a personal history of diabetes and sensorineural hearing loss could suggest mitochondrialopathies.55,56 If genetic causes are unlikely or have been without success by performing genetic tests, other non-genetic disorders should be considered. Myocarditis is the most common cause among them and could be related or non-related to infections.

A recent history of unknown fever and travels in foreign countries could suggest an infective myocarditis, while a personal history of autoimmune diseases or signs and symptoms of systemic inflammatory disorders can suggest a non-infective myocarditi-
tis. Some symptoms and signs may suggest a specific cause of DCM (Table 2): the presence of intellectual disability may suggest a mitochondrial cause\(^1\) and dystrophinopathies;\(^5\) sensorineural deafness in mitochondrialopathies;\(^5\) gait disturbance and muscle weakness in neuromuscular diseases;\(^5\) pigmentation of skin and scars is a specific sign of hemochromatosis.\(^5\)

The ECG in DCM shows usually less clues than other cardiomyopathies (Table 2).\(^6\) An acute AV block presentation may suggest myocarditis, while a chronic stable form suggests cardiac sarcoidosis or genetic causes (laminopathies, desminopathies, myotonic dystrophy). A premature paroxysmal AF may be a manifestation of SCN5A mutation,\(^5\) laminopathies\(^5\) or polygenic disorder.

The echocardiogram in DCM does not give many red flags (Table 2): a phenotype that meet the diagnostic criteria for left ventricular non-compaction (LVNC), does arise the suspicion of a genetic form of DCM; a mild dilatation, in presence of akynetic segments with non-coronary distribution, may be present in myocarditis and cardiac sarcoidosis; a dilated LV with posterolateral akynesis, in absence of CAD, suggests a dystrophin-related cardiomyopathy.\(^3,4,49,60\)

Some laboratory tests may help in differential diagnosis of genetic and non-genetic causes of DCM (Table 2).\(^3,4,49,60\) Usually the diagnostic pathway is completed, at least, by the execution of a cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) and 48-h ECG Holter monitoring. The CMR may show: a dilated LV with global hypokinesis, reduced ejection fraction and non-coronary LGE distribution in non-ischaemic cardiomyopathies;\(^61,62\) the presence of extensive oedema on T2 mapping is a red flag for inflammatory myocarditis;\(^63\) the akynesis of basal septum with presence of LGE suggests a cardiac sarcoidosis;\(^64\) a short T\(_2^*\) may suggest a myocardial iron overload for its highly sensitivity in detecting myocardial iron deposition.\(^65\) The 24-h ECG monitoring may show the presence of some arrhythmias potentially responsible for forms of reversible LV dysfunction known as tachycardia-induced cardiomyopathies.\(^66\) Cardiac scintigraphy\(^67,68\) and/or endomyocardial biopsy (EMB)\(^69,70\) are sometimes necessary to achieve the diagnosis. A positive cardiac 18F-FDG-PET scan, in the suspicion of an inflammatory cardiac involvement, can reinforce the hypothesis of inflammatory-induced myocarditis.

**Second clinical scenario**

A 53-year old woman was admitted to our Department due to the sudden onset of shortness of breath on minimal exertion and palpitations.

She had no family history for cardiovascular disorders, and reported a personal history of autoimmune disorders such as Hashimoto’s thyroiditis, vitiligo and psoriatic arthritis. The careful physical examination showed only mild ankle swelling. The

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**Figure 1.** A) ECG showing T-wave inversion in precordial and lateral leads; B) Low image quality transthoracic echocardiography: apical 4-chamber view showing an apical mass d; C) Contrast echocardiography with lung penetrating agent showing apical hypertrophy.
Table 1. Diagnostic clues fostering the suspicion of specific causes of hypertrophic and restrictive cardiomyopathies.

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
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<th>Cardiac magnetic resonance</th>
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<tr>
<td><strong>Amyloidosis</strong> (HCM, RCM)</td>
<td>Sensory abnormality, carpal tunnel syndrome, skin alterations, vitreous opacities (ATTR).</td>
<td>Voltage discordance pattern, pseudonarcrection pattern, abnormal QRS axis deviation, AF, conduction abnormalities, IV blocks.</td>
<td>Concentric LVH with preserved LV size, restrictive filling pattern, biventricular enlargement, thickened IV valves, pericardial effusion, apical sparing pattern on longitudinal strain imaging.</td>
<td>Morphology described in US. Typical signal changes in T1-w imaging diffuse circumferential LGE pattern involving the subendocardium, ECV quantification on T1 mapping. Kidney function, proteinuria, urine and plasma protein immunofixation with free light chains.</td>
</tr>
<tr>
<td><strong>Danon disease</strong> (HCM, RCM)</td>
<td>Intellectual disability, retinal dysfunction, optical atrophy, proximal skeletal myopathy.</td>
<td>Marked QRS voltages, short PR with pre-excitation.</td>
<td>Marked LVH. Marked LVH with LGE involving LV wall(s) and RV insertion point(s).</td>
<td>Creatin kinase, liver function</td>
</tr>
<tr>
<td><strong>Fabry disease</strong> (HCM, RCM)</td>
<td>Cataracts, corneal opacities, corneal verticillata, sensorineural deafness, angiorkeratoma, hypo or hyperidrosis, sensory abnormalities, TIA/ictus.</td>
<td>Short PR, conduction abnormalities, IV blocks.</td>
<td>Concentric LVH or B VH, mild aortic root dilatation, possible binary appearance of the endocardial border.</td>
<td>Concentric LVH, midwall or subepicardial LGE of mid-to-basal interventricular wall, fats lowers T1 values. Renal function.</td>
</tr>
<tr>
<td><strong>Friedreich’s ataxia</strong> (HCM)</td>
<td>Gaits disturbance, optic atrophy.</td>
<td>AF</td>
<td>Variable LVH pattern with normal cavity and EF</td>
<td>Concentric LVH with aspecific midwall LGE</td>
</tr>
<tr>
<td><strong>Haemochromatosis transferrin</strong> (HCM, RCM)</td>
<td>Liver cirrhosis, diabetes mellitus, hypogonadotropic hypogonadism, arthritis. Skin and scars pigmentaton.</td>
<td>Normal QRS or low voltages, repolarization abnormalities in advanced stages.</td>
<td>LVH or B VH with dilated cystes and global dysfunction in late stage, restrictive physiology.</td>
<td>Shortened T2* values. Serum iron, saturation and ferritin.</td>
</tr>
<tr>
<td><strong>LEOPARD syndrome</strong> (HCM)</td>
<td>Lentigines, ocular hypertelorism, abnormalities of the genitalia, short stature, sensorineural deafness.</td>
<td>Short PR.</td>
<td>Asymmetric LVH and RV involvement, RVOT obstruction with pulmonary stenosis.</td>
<td>Aspecific LGE distribution.</td>
</tr>
<tr>
<td><strong>Mitochondrial diseases</strong> (HCM, RCM)</td>
<td>Intellectual disability; retinal and/or optic nerve disease; palpebral ptosis; muscle weakness.</td>
<td>Short PR with pre-excitation.</td>
<td>Concentric LVH, LV dilation and dysfunction in late stage.</td>
<td>CPEO/KSS: intramural pattern of LGE, MELAS: diffusely distributed LGE. Creatin kinase, liver function, myoglobinuria, lactic acid levels.</td>
</tr>
<tr>
<td><strong>Mucopolysaccharidoses</strong> (HCM, RCM)</td>
<td>Intellectual disability, coarse facies, visual impairment, hearing loss, hypertrichosis, skeletal abnormalities.</td>
<td>Low QRS voltages.</td>
<td>ASH pattern with valcular thickening, mitral prolapse.</td>
<td></td>
</tr>
<tr>
<td><strong>Pompe disease</strong> (HCM, RCM)</td>
<td>Muscle weakness, respiratory failure.</td>
<td>Marked QRS voltages; short PR with pre-excitation.</td>
<td>Marked LVH.</td>
<td>Creatin kinase, liver function.</td>
</tr>
<tr>
<td><strong>PRKAG2 mutation</strong> (HCM)</td>
<td>Unexplained syncope.</td>
<td>Short PR with pre-excitation, conduction abnormalities.</td>
<td>Variable wall thickness, PH, RV involvement, normal to dilated ventricular cystes, ventricular aneurysms, focal or global hypokinesia, restrictive physiology.</td>
<td>Serum amyloid A, soluble IL-2R, lysozyme, ACE, glycoprotein KL-6, hypercalcruia.</td>
</tr>
<tr>
<td><strong>Sarcoidosis</strong> (RCM)</td>
<td>SCID.</td>
<td></td>
<td>Variable wall thickness, PH, RV involvement, normal to dilated ventricular cystes, ventricular aneurysms, focal or global hypokinesia, restrictive physiology.</td>
<td>Akynesia of basal septum with LGE, variable extent of myocardial fibrosis (LGE) and oedema (T2-w imaging), granulomas within walls.</td>
</tr>
</tbody>
</table>

AATR, TTR-related amyloidosis; ACE, angiotensin converting enzyme; AF, atrial fibrillation; ASH, asymmetrical septal hypertrophy; IV, atrio-ventricular; B VH, biventricular hypertrophy; CPEO, chronic progressive external ophthalmoplegia; ECV, extracellular volume; EF, ejection fraction; IV, intraventricular; IV, interventricular; KSS, Kearns-Sayre syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosi, stroke-like episodes; LGE, late gadolinum enhancement; LV, left ventricular; LVH, LV hypertrophy; PH, pulmonary hypertension; RV, right ventricular; RVOT, RV outflow tract; SCD, sudden cardiac death; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.
laboratory tests demonstrated significantly increased erythrocyte sedimentation rate (ESR) and C-reacting protein (CRP), and mild anaemia. The ECG showed sinus rhythm, with no conduction or repolarization abnormalities. The echocardiogram showed mild left ventricular dilatation with global hypokinesis and moderately reduced systolic fraction (EF ~45%) (Figure 2A).

A coronary cause was excluded performing a coronary angiogram, which was unremarkable. Other possible causes were excluded performing a CMR (Figure 2B) that showed mild and patchy areas of myocardial oedema on T2-weighted imaging and non-coronary distribution of LGE in midwall. In absence of other clinical findings suggesting a specific cause, our diagnostic suspicion was oriented towards a non-genetic cardiomyopathy: the personal history of autoimmune disorders, the sudden onset of symptoms and the increase of inflammatory markers all suggested an inflammatory cardiomyopathy. Furthermore, the LGE pattern prompted to consider a differential diagnosis between myocarditis and cardiac sarcoidosis.

The 18F-FDG-PET scan, performed to evaluate a possible cardiac inflammation, showed a mild and diffuse LV enhancement (Figure 2C). The EMB was performed but was non-conclusive. In this case we concluded for a probable inflammation-induced cardiomyopathy, in a patient with a significant history of autoimmunity. Furthermore, the LGE pattern prompted to consider a differential diagnosis between myocarditis and cardiac sarcoidosis. The 18F-FDG-PET scan, performed to evaluate a possible cardiac inflammation, showed a mild and diffuse LV enhancement (Figure 2C). The EMB was performed but was non-conclusive. In this case we concluded for a probable inflammation-induced cardiomyopathy, in a patient with a significant history of autoimmunity. Furthermore, the LGE pattern prompted to consider a differential diagnosis between myocarditis and cardiac sarcoidosis.

The causes of RCM can be classified in genetic and acquired. RCM can be grouped, based on causative classification, in four main categories: interstitial fibrosis (idiopathic RCM, sarcomeric RCM, diabetic RCM, diab-

Restrictive phenotype

Restrictive cardiomyopathy is defined as restrictive ventricular physiology in presence normal or reduced systolic and diastolic volumes of one or both ventricles, and normal ventricular wall thickness. It represents the most difficult phenotype to approach in the field of cardiomyopathy because it is physiology-based, because the restrictive pattern of ventricular filling (rapid raise in ventricular pressures in presence of small increase in volume) due to the myocardial stiffness shows itself only in the late phases of the disease, and the boundary between the hypertrophic and the restrictive phenotype is somehow vague.

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Figure 2. A) Apical 4-chambers view on echocardiography showing left ventricular dilatation; B) Left ventricular dilatation confirmed on cardiac magnetic resonance image; C) Mild and diffuse left ventricular enhancement showed on 18F-FDG-PET scan.
ic cardiomyopathy, infiltrative disorders (amyloidosis predominantly), storage diseases (haemochromatosis, glycogenosis, desminopathies, etc.) and endomyocardial diseases (endomyocardial fibrosis, hypereosinophilia syndrome, drugs, etc.).

Thus, when the suspicion of RCM arises from a preliminary evaluation, some red flags could help us in identifying a specific cause.

About signs and symptoms, few specific clues should be considered (Table 1): the intellectual disability may suggest the Noonan syndrome; sensory abnormality, paraesthesia and/or carpal tunnel syndrome, are common in amyloidosis, especially in AL form; a history of muscle weakness is typical in desminopathies.

The ECG (Table 1) may show AV block especially in amyloidosis and in desminopathies.

The echocardiogram (Table 1) may show an incomplete ventricular apical obliteration in endomyocardial fibrosis and hypereosinophilia syndrome.

The laboratory tests usually performed are listed in Table 1.

### Third clinical scenario

A 67-year old woman was admitted to our Division due to the acute onset of dyspnoea on mild exertion, peripheral oedema, dizziness and oliguria. The family history was unremarkable. She had a personal history of hypertension, diabetes mellitus with chronic kidney disease and bilateral carpal tunnel syndrome.

On physical examination diminished sounds with S3 gallop and mitral systolic murmurs were heard, jugular venous pressure (JVP) was raised and peripheral bilateral pitting oedema was noticed. The laboratory studies showed severe kidney failure with proteinuria and very high values of NT-proBNP and troponin I. The ECG revealed low QRS voltages in limb leads and poor R-wave progression in the chest leads (Figure 3A). A brief and asymptomatic III degree AV block with spontaneous recovery to sinus rhythm was recorded on the 24-h ECG monitoring. The echocardiography showed concentric left ventricular hypertrophy, normal ejection fraction with low TDI velocities (Figure 3B), diffuse thickening of interatrial septum and atrioventricular valves, moderate pulmonary hypertension, restrictive pattern of diastolic LV filling and severe left atrial dilatation.

Some diagnostic red flags emerged: a history of bilateral carpal tunnel syndrome; a typical ECG pattern; a concentric biventricular hypertrophy with valvular involvement on echocardiogram. All these

Figure 3. A) ECG showing a pseudo-infarct pattern; B) Transthoracic echocardiography showing restrictive filling pattern at mitral inflow spectral Doppler signal and low systolic and diastolic peak velocities on tissue Doppler imaging; C) Apical sparing pattern showed on speckle tracking imaging.
clues fostered the hypothesis of cardiac amyloidosis.

Various forms of amyloidosis exist and in each one the myocardial involvement is variable. When the suspicion of cardiac amyloidosis is present other diagnostic techniques can be used: cardiac MRI\textsuperscript{86-88} and 99mTc-DPD scan\textsuperscript{89-91} are sensitive tests for the detection, characterization and differentiation of forms of cardiac amyloidosis. The 99mTc-DPD scan is an exquisite test for the transthyretin-related amyloidosis (ATTR) diagnosis, far less sensitive in AL amyloidosis. However, we could not perform either cardiac MRI in this patient, because she was strongly claustrophobic, nor the 99mTc-DPD scan, because the test was not available at that time in our Department.

An echocardiogram with the speckle tracking analysis was repeated and showed the typical relative apical sparing pattern,\textsuperscript{92} specific for cardiac amyloidosis (Figure 3C).

In order to support our diagnostic hypothesis, second level laboratory tests, consisting of urine and plasma protein immunofixation with free light chains, were performed and revealed elevated free $\lambda$ light chains in blood and urine.

 Nonetheless, a definitive diagnosis of amyloidosis requires histological evidence of specific amyloid deposition on tissue specimens. Thus some biopsies with increasing degree of invasiveness were obtained. Fat pad biopsy stained negatively for amyloid with Congo red on polarizing microscopy but electron microscopy showed some fibrils formed by amyloid in small blood vessels. Moreover, immunoelectron microscopy permitted further characterization of the patient’s amyloid $\lambda$ free chains.

In this case we concluded for AL amyloidosis with severe heart involvement in the form of a restrictive cardiomyopathy, due to monoclonal gammopathy of undetermined significance (MGUS). Than, a specific therapy with steroids and Bortezomib started (Figure 4).

**Right ventricular cardiomyopathies**

The right ventricular cardiomyopathies are myocardial disorders in which the right ventricular involvement is exclusive or predominant.\textsuperscript{93} Under this umbrella-term are grouped several disorders: inherited disorders, such as the arrhythmogenic right ventricular cardiomyopathy (ARVC), the endomyocardial fibrosis (EMF), the cardiac sarcoidosis and the cardiac amyloidosis. Also in acute myocarditis may mimic ARVC when it displays prevalent RV involvement.

In RV cardiomyopathies, the family history is important: the presence of family members affected and a family history of SCD or ICD implantation in pedigree analysis fosters the suspicion of ARVC.\textsuperscript{94,95} A personal history of ventricular tachycardia (VT) or ICD implantation in secondary prophylaxis is consistent with disorders such as ARVC, amyloidosis, sarcoidosis and myocarditis. No specific symptoms are known and the most of these conditions are asymptomatic or poorly symptomatic.

The physical examination gave specific clues just in ARVC (Table 2): the presence of palmoplantar keratoderma and woolly hair is typical in Naxos disease and in Carvajal syndrome,\textsuperscript{96} clinical variants of ARVC.

Conversely, the ECG is a sensible tool that may present some diagnostic clues (Table 2): repolarisation abnormalities, such as inverted T waves in inferolateral leads, and intra-ventricular conduction delays, represented by $QRS$ enlargement and epsilon waves, are useful red flags for ARVC diagnosis.\textsuperscript{97,98} In amyloidosis there

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**Figure 4.** A) ECG showing an epsilon wave widespread with T-wave inversion on inferolateral leads; B) Transthoracic echocardiography: apical 4-chamber showing markedly dilated right cavities.
are not clues specific for the RV involvement. The bundle branch blocks may be present in ARVC, congenital heart disorders, amyloidosis, cardiac sarcoidosis and myocarditis for different reasons.

The signal average ECG is a wide amplitude superficial ECG that permits to recognize the low amplitude late potentials at the end of the QRS complex.99 The late potentials are a hallmark of ARVC and help us in disease definition and in the differential diagnosis with mimicking conditions.

The echocardiogram is the first cardiovascular imaging method usually performed100 but, for the clearest visualization of the RV, the best spatio-temporal resolution and possible myocardial characterization gave by the gadolinium administration, the CMR represents an indispensable tool in this setting (Table 2). In ARVC the tissue analysis shows on T1 weighted images the myocardial fatty infiltration, a specific diagnostic clue observed as areas of high signal intensity.101,102 In the early stage of EMF are frequently described isolated thrombi or RV apical obliteration, as a manifestation of massive endomyocardial thrombus formation, with RV diastolic dysfunction and tricuspid valve involvement, while the tissue analysis shows a typical circumferential sub-endocardial hyperenhancement. In the later stage, the cavity obliteration extends over the apex disorganizing the ventricular architecture: a severe spontaneous contrast in RV cavity and a giant right atrium are then described.103 In cardiac amyloidosis, sarcoidosis and myocarditis the CMR findings are the same described for the dilated phenotype.

The laboratory tests usually performed in this setting are listed in Table 2.

As for other cardiomyopathies, diagnostic techniques may be necessary to achieve the diagnosis: the cardiac nuclear scintigraphy and the endomyocardial biopsy.

Table 2. Diagnostic clues fostering the suspicion of specific causes of dilated and right ventricular cardiomyopathies.

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<tr>
<th>Clinical manifestations</th>
<th>ECG</th>
<th>US</th>
<th>CMR</th>
<th>Laboratory tests</th>
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<tr>
<td>ARVC</td>
<td>Palmpoplantar keratoderma and woolly hair (Naxos and Carvajal syndromes).</td>
<td>IV blocks, QRS widening, inverted T-waves on precordial leads, epsilon wave in inferolateral leads, VT.</td>
<td>RV segmental or global dilation with systolic dysfunction and/or aneurysms, sacculations or trabeculae, possible LV involvement.</td>
<td>Morphological RV anomalies (aneurysms, sacculations, trabeculae), regional or diffuse akinesia, presence of fibrosis on LGE and fat, possible LV involvement.</td>
</tr>
<tr>
<td>Muscular-related diseases</td>
<td>Intellectual disability (dystrophin-related disease, FXTN gene mutation).</td>
<td>Stable AV block (desminopathies, laminopathies and myotonic dystrophy), paroxysmal AF (laminopathies, myotonic dystrophy).</td>
<td>Dilated LV or biventricular involvement with progressive dysfunction. Dilated LV with posterolateral akinesia (dystrophin-related disease).</td>
<td>Dilated LV or biventricular involvement with progressive dysfunction. Variable extent of LGE.</td>
</tr>
<tr>
<td>Mitochondrial diseases</td>
<td>Fatigue with nearly normal ejection fraction, intellectual disability, sensorineural deafness, and palpebral ptosis.</td>
<td>Short PR with pre-excitation.</td>
<td>Concentric LVH, LV dilation and dysfunction in late stage.</td>
<td>CPEO/KSS: intramural pattern of LGE, MEAS: diffusely distributed LGE.</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>Liver cirrhosis, diabetes mellitus, hypogonadotropic hypogonadism, arthritis, pigmentation of skin and scars.</td>
<td>Normal QRS or low voltages, repolarization abnormalities in late stage.</td>
<td>LVH or BVH with dilated cavities in late stage, restrictive physiology.</td>
<td>Shortened T2*.</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>SCF, SCD.</td>
<td>Posteroextensive infarction, conduction abnormalities, IV blocks, ventricular arrhythmias (VT, VF).</td>
<td>Variable wall thickness, PH, RV involvement, normal to dilated cavities, ventricular aneurysms, focal or global hypokinesis, restrictive physiology.</td>
<td>Akinesia of basal septum with LGE, oedema on T2-w imaging, granulomas within ventricular walls.</td>
</tr>
</tbody>
</table>

ARVC, arrhythmogenic right ventricular cardiomyopathy; ACE, angiotensin converting enzyme; AF, atrial fibrillation; IL, infarct ventricular; BVH, biventricular hypertrrophy; CPEO, chronic progressive external ophtalmoplegia; K, interventricular; KSS, Kearns-Sayre syndrome; mitochondrial encephalopathy, lactic acidosis, stroke-like episodes; LGE, late gadolinium enhancement; LV, left ventricular; DH, LV hypertrophy; PH, pulmonary hypertension; RV, right ventricular; SCD, sudden cardiac death; VT, ventricular fibrillation; VF, ventricular tachycardia.

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sy are often required for the differential diagnosis.

Fourth clinical scenario

A 62-year old man was visited in our ambulatory due to the recent onset of shortness of breath, tiredness and peripheral oedema. He had a previous cardiologic consultation in which a biventricular systolic dysfunction was noticed on echocardiogram. He had a family history of CAD and sudden cardiac death on his paternal side of the family. In his personal history he had a treated hypothyroidism and an ICD implantation two years before, following an episode of syncope with evidence of ventricular tachycardia on ECG.

On physical examination raised JVP and marked bilateral ankle swelling were noticed.

The ECG showed paced rhythm with normal AV, epsilon wave widespread with normal R-wave progression and T-wave inversion on anterior and inferior leads.

The echocardiogram showed a markedly dilated RV cavity with severely impaired systolic function; mildly impaired LV function (EF 45%), mainly due to abnormal septal motion; moderate tricuspid regurgitation, due to a combination of dilated RV annulus and ICD lead, causing coaptation defect, with high pulmonary pressure and severely dilated RA.

A coronary angiogram was performed previously, after the syncopal episode, and was unremarkable. The laboratory screening showed raised inflammatory markers.

Based on the clinical approach, a biventricular myocardial disorder with a predominant RV involvement, was suspected. The conditions considered were ARVC, cardiac sarcoidosis and myocarditis. The family history of SCD and the personal history of ICD implantation due to VT were suggestive of an inherited and potentially arrhythmogenic disorder, mainly ARVC, but did not exclude the other possible diagnosis. The complaint of dry cough, in presence of normal chest X-ray and in absence of other causes immediately excluded, suggested the diagnosis of cardiac sarcoidosis. The epsilon waves and the inverted T-waves in inferolateral leads were specific of other causes immediately excludible, with high pulmonary pressure and severely dilated RA.

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References


