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Cardiac amyloidosis: the great pretender

Claudio Rapezzi[1,4] · Massimiliano Lorenzini[1] · Simone Longhi[1] · Agnese Milandri[1] · Christian Gagliardi[1] · Ilaria Bartolomei[2] · Fabrizio Salvi[2] · Mathew S. Maurer[3]

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Abstract Cardiac amyloidosis (CA) is often misdiagnosed because of both physician-related and disease-related reasons including: fragmented knowledge among different specialties and subspecialties, shortage of centres and specialists dedicated to disease management, erroneous belief it is an incurable disease, rarity of the condition, intrinsic phenotypic heterogeneity, genotypic heterogeneity in transthyretin-related forms and the necessity of target organ tissue histological diagnosis in the vast majority of cases. Pitfalls, incorrect beliefs and deceits challenge not only the path to the diagnosis of CA but also the precise identification of aetiological subtype. The awareness of this condition is the most important prerequisite for the management of the risk of underdiagnoses and misdiagnosis. Almost all clinical, imaging and laboratory tests can be misinterpreted, but fortunately each of these diagnostic steps can also offer diagnostic "red flags" (i.e. highly suggestive findings that can foster the correct diagnostic suspicion and facilitate early, timely diagnosis). This is especially important because outcomes in CA are largely driven by the severity of cardiac dysfunction and emerging therapies are aimed at preventing further amyloid deposition.

✉ Claudio Rapezzi
claudio.rapezzi@unibo.it

[1] Cardiology, Department of Experimental, Diagnostic and Specialty Medicine – DIMES, Alma Mater Studiorum, University of Bologna, Bologna, Italy

[2] IRCCS Neurosciences, Bologna, Italy

[3] Center for Advanced Cardiac Care, Columbia College of Physicians and Surgeons, New York City, NY, USA

[4] Istituto di Cardiologia, Policlinico S. Orsola-Malpighi, via Massarenti 9, 40138 Bologna, Italy

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Introduction

Amyloidosis refers to a large group of disorders caused by extracellular deposition of insoluble abnormal fibrils composed of misfolded proteins, which can alter tissue structure and impair function of multiple organs including the heart [1]. Cardiac deposition is associated with diastolic and systolic dysfunction, rhythm disturbances and ischaemia. The overall myocardial damage is due to both tissue infiltration and direct toxicity of circulating preamyloid proteins, particularly in case of immunoglobulin light-chain (AL) amyloidosis in which amyloidogenic light chains can be toxic to cardiac myocytes [1, 2]. Amyloidosis may be acquired or hereditary; it is classified according to the nature of the fibril precursor protein and the clinical features (Table 1) [3]. Immunoglobulin light-chain and transthyretin (TTR)-related are the most frequent types of systemic amyloidosis encountered in the clinical setting.

AL amyloidosis is the most frequently diagnosed type in a referral centre; 0.3 cases per 100,000 population are diagnosed annually [2]. All patients with cardiac AL amyloidosis have a plasma cell dyscrasia. Although this is a clonal plasma cell disorder, the majority of patients do not have multiple myeloma and the average bone marrow plasma cell content is 5–7 % [1, 2]. Nearly 80 % of patients with cardiac AL amyloidosis have λ light chain (compared with κ light chain)-related disease.

Among the more than 20 known precursor proteins capable of forming amyloid fibrils in vivo, transthyretin can

Table 1 Classification of cardiac amyloid types most frequently encountered in humans

Amyloid protein	Precursor	Main features	Myocardial involvement
AL	Immunoglobulin light chain	Primary/myeloma associated	Frequent
ATTR	Transthyretin	Familial	Variable according to genotype
ATTR	Transthyretin	Wild type	Constant
AApo AI	Apolipoprotein AI	Familial	Occasional but severe
AApo AII	Apolipoprotein AII	Familial	Exceptional
AFib	Fibrinogen α chain	Familial	Exceptional
ALys	Lysozyme	Familial	Exceptional
AA	Serum AA	Secondary, reactive	Exceptional
A β2 M	β2 microglobulin	Hemodyalisis associated	Exceptional
IAA	Atrial natriuretic factor	Atrial fibrillation	Atrial tissue

Modified from Sipe et al. [3]

AL, immunoglobulin light-chain amyloid; ATTR, transthyretin-related amyloid; AApoAI, apolipoprotein A-I amyloid; AApoAII, apolipoprotein A-II amyloid; Afib, fibrinogen alpha chain amyloid; ALys, lysozyme amyloid; AA, amyloid A; A β2M, β2 microglobulin amyloid; IAA, isolated atrial amyloid

lead to two distinct forms of cardiac amyloidosis (CA): hereditary (caused by mutations in the TTR gene) and wild-type (wt) TTR ("systemic senile amyloidosis"). TTR-related (ATTR) CA is currently diagnosed with increasing frequency because of the emerging role of "bone tracers" scintigraphy and the willingness of cardiologists to perform endomyocardial biopsies in order to allow patients inclusion in prospective clinical trials with disease-modifying agents [2, 4]. The general impression in referral centres is that wtTTR CA could even be the most common type of amyloidosis.

A recent international registry (THAOS) that enrolled >2000 patients with TTR-related amyloidosis shows that Val30Met is the most frequent TTR mutation in patients who received a diagnosis of ATTR, causing the disease historically known as "type I FAP" [5, 6]. The largest cluster of individuals with ATTR caused by the Val30Met mutation may be found in northern Portugal [7], where the incidence is estimated to be one in 538 individuals [8]. In the USA, V122I is the most frequent cause of hereditary ATTR (prevalence ranging 3–3.9 % in African Americans) [9], leading to a late onset CA or to an increased risk of incident heart failure among African Americans [10].

In Europe, the overall prevalence of ATTR is estimated to be less than one in 100,000 individuals [8]. In endemic areas of northern Sweden (Piteå and Skelleftå), the frequency of the Val30Met mutation is 4 %; however, the penetrance is relatively low (11 % by 50 years). Conversely, in Portugal, the penetrance is high (80 % by 50 years). Although endemic in some areas of Japan, the prevalence of TTR is estimated to be lower than in Europe, at approximately one in 1,000,000 individuals [8].

Potential for misdiagnosis: physician- and disease-related factors

Cardiac amyloidosis is often misdiagnosed as another condition or delayed in its recognition as a result of both physician-related and disease-related reasons (Table 2) [2]. First, the management of amyloidosis is not confined to a single specialty but is fragmented among different specialties and subspecialties including neurology, nephrology, haematology and cardiology. Indeed, both physicians and centres fully dedicated to the management of the disease are still relatively few. For many years, clinical research on CA has been held back by the limited effectiveness of available haematological treatment for AL and by the absence of disease-modifying therapy for ATTR.

Regarding disease-related factors, systemic amyloidosis is not only rare but also phenotypically heterogeneous, and this pathophysiological, morphological and clinical variability frequently leads to misdiagnosis in the various settings where the patient presents or is referred. Clinical presentation is highly variable in both AL and ATTR; moreover, cardiac AL amyloidosis is a systemic disease rather than an isolated cardiomyopathy, where half of the patients also have renal involvement, 1/6 have liver involvement, and approximately 1/10 have relevant peripheral neurological involvement [2]. In ATTR, phenotypic heterogeneity is even greater when considering the worldwide disease profile. Many factors can explain this variability including: genetic heterogeneity, geographical area, ethnicity, endemic versus non-endemic aggregation, age, gender, gender of the transmitting parent and probably

Table 2 Factors leading to misdiagnosis

Physician-related factors
Fragmented knowledge among different specialties and subspecialties
Shortage of centres and experts dedicated to specialised disease management
Common misconceptions about diagnosing and typing amyloid
• Low voltage is not sensitive nor specific finding in isolation to exclude the presence of cardiac amyloidosis
• Serum protein electrophoresis is not a sufficient screening test to exclude the presence of a plasma cell disorder than can cause AL amyloid
• A fat pad biopsy has a sensitivity for AL amyloid of 70 % at best and is positive in < 50 % of subjects with ATTR CA
Erroneous belief it is an untreatable disease
Disease-related factors
Rarity
Intrinsic phenotypic heterogeneity
Genotypic heterogeneity in ATTR
Necessity of target organ tissue histological diagnosis in the vast majority of cases

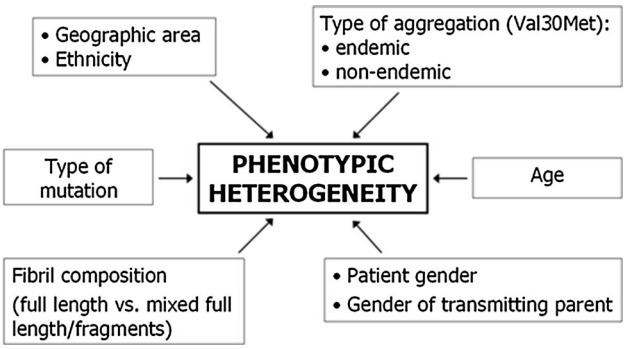

Fig. 1 Main known determinants of phenotypic heterogeneity in ATTR. Modified from Rapezzi et al., Nat Rev Cardiol 2010

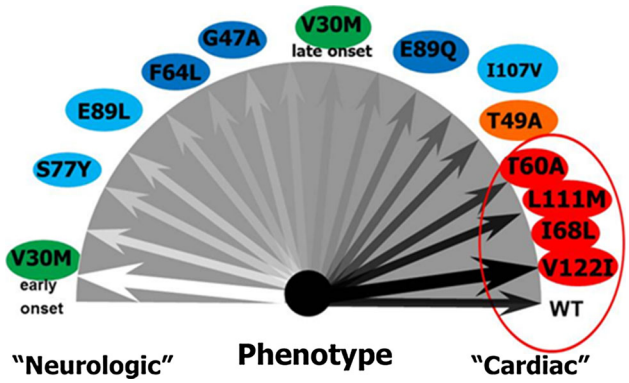

Fig. 2 Genotype–phenotype correlation in ATTR. Modified from Rapezzi et al., Eur Heart J 2013

amyloid fibril composition (Fig. 1) [11]. V30M is the only pathogenic mutation that has large foci around the world, especially in parts of Portugal, Japan and northern Sweden [5, 6, 8, 11]. The prominent features of Portuguese and Japanese endemic Val30Met are sensorimotor polyneuropathy—usually starting in the mid-thirties—and autonomic neuropathy [5, 6, 8, 11]. Family history is generally positive, as the condition is inherited in an autosomal dominant fashion. Conduction disturbances are relatively frequent; on the contrary, cardiomyopathy is rare, but can lead to heart failure as disease progresses [5, 6, 8, 11]. On the other hand, the clinical profile of Swedish endemic Val30Met ATTR is characterised by older age at onset, lower (about 2 %) penetrance and a slower disease progression [5, 6, 8, 11]. Non-endemic forms of Val30Met are found in many countries and have a much greater phenotypic variability. A common characteristic is lower age-related penetrance with an apparently negative family history. Cardiomyopathy tends to be more frequent than in endemic Val30Met, whereas autonomic dysfunction is generally milder [5, 6, 8, 11]. Non-Val30Met mutations have been reported in different European countries, in Japan, in North and South America [5, 6, 8, 11]. Many mutations tend to cluster in certain ethnic groups and in limited geographical areas, in relation to the existence of common founders ("private mutations"). In general, a relatively tight genotype–phenotype association can be found (Fig. 2) [12]. Some mutations are associated with both neurological and cardiac manifestations, whereas others lead to an exclusively neurological disease and a small number are associated with an exclusively cardiological phenotype. In ATTR, particularly in Val30Met-related form, age at onset is quite variable and unknown factors, other than the mutation, may be involved, including gender of the transmitting parent [11]. In patients originating from Portuguese, Swedish and some Japanese kindreds, age at onset is significantly later when the mutation is inherited from the mother than from the father. Patient gender can also influence cardiac phenotype since female gender seems to provide some protection from myocardial involvement, at least before menopause onset

[11, 13]. The phenotype of Val30Met ATTR may also be influenced by amyloid fibril composition: fibrils composed only of full-length TTR seem to be associated with early age onset without clinical cardiac involvement, whereas mixtures of full-length and fragmented TTR fibrils have been associated with late onset and signs of cardiac involvement [14].

Another factor that can potentially lead to an incomplete, wrong or late diagnosis is the necessity of a histological demonstration of target organ amyloid infiltration as the diagnostic gold standard. This means that in cases with an exclusively cardiac phenotype (in particular, wild-type ATTR), endomyocardial biopsy is frequently unavoidable. However, this procedure is usually restricted to large referral centres with cardiac transplant capacities and requires pathologist expert in interpretation.

Pitfalls and deceits (but also diagnostic red flags)

Pitfalls and deceits are present all along the path that leads from the initial suspicion to the diagnosis of CA, to the precise aetiological classification. Almost all clinical, imaging and laboratory tests can often be misinterpreted, but fortunately each of these diagnostic steps can also offer diagnostic "red flags", i.e. highly suggestive findings that can foster the correct diagnostic suspicion [15].

Clinical history/physical examination

In both AL- and TTR-related disease, exclusive cardiac involvement is the exception rather than the rule. This leads patients with CA to often seek medical attention for neurological, renal or ophthalmological rather than cardiological issues. The possibility of multisystemic involvement has been (excessively) emphasised in many medical textbooks leading many physicians to consider the diagnosis of amyloidosis only in the presence of extracardiac findings such as macroglossia and purpura of the eyelids. Unfortunately, these highly specific signs are only present in a minority of AL cases [2, 15].

Regarding hereditary ATTR, a frequent pitfall is due to the fact that an obvious family history is spontaneously reported by the patient only in a minority of cases. This is due to the late and incomplete penetrance of the mutations responsible for the forms with a prevalently cardiac phenotype.

On the other hand, a clinical examination guided by a cardiomyopathy-oriented mindset [15] can offer a number of diagnostic red flags that can orient towards a correct final diagnosis in a patient presenting with a hypertrophic phenotype. Useful findings include carpal tunnel syndrome in ATTR (particularly if bilateral in a male), history of unexplained neuropathic pain, orthostatic hypotension and a diagnosis of "hypertrophic cardiomyopathy" after the sixth decade.

Laboratory tests

No blood test can diagnose ATTR; in particular, dosage of circulating TTR is not useful for clinical purposes. In AL, the plasma cell clone is small and standard serum protein electrophoresis is abnormal only in 60–70 % of cases and is therefore not sensitive enough to identify the presence of a plasma clone that could cause AL amyloid. Serum and urine immunofixation and quantification of serum free light chains are required in order to reveal clonal activity, and the combination of these three tests has >99 % sensitivity for identifying a plasma clone that is universally associated with the presence of AL cardiac amyloid. Unfortunately, a moderate increase in circulating free light chains is not necessarily pathological, since up to 5 % of the "normal" population aged >65 have so-called MGUS (monoclonal gammopathy of undetermined significance, a condition that can evolve into different haematological diseases over time but can also remain non-pathological) [16]. One of the most frequent pitfalls is the misdiagnosis of AL CA in elderly patients with TTR-related amyloidosis and MGUS (up to 10 % of misdiagnosis even in referral centres) [2, 17]. Conversely, it is rarely (<1 %) possible for immunofixation and free light chain levels to be normal in the presence of AL amyloidosis.

Plasma levels of natriuretic peptides (BNP and NT-proBNP) tend to be particularly high in CA, frequently out of proportion to the hemodynamic burden [16]. This is probably due to the direct toxicity of pre-amyloid proteins at myocardial cellular level. The same mechanism frequently produces an elevation of troponins. It is therefore not infrequent that a patient with CA hospitalised for heart failure receives a first, erroneous, diagnosis of acute coronary syndrome. On the other hand, the particularly high levels of troponin or natriuretic peptides can be a red flag. A typical example is the case of an elderly patient with an echocardiographic diagnosis of hypertrophic cardiomyopathy in whom increased serum troponin, often interpreted as being due to coronary ischaemia and leading to inappropriate treatment, should lead to the suspicion of AC. The same applies for proteinuria which can be a red flag for AL cardiac amyloid in a patient with a hypertrophic phenotype [15].

Electrocardiogram

The standard ECG has traditionally offered the most popular screening test for AC with a low QRS voltages in spite of a hypertrophic left ventricle [11, 15, 18]. In contemporary large series, however, the frequency of this finding has been found to be strictly linked to aetiology and ranges

from 60 % in AL to 20 % in ATTR [19, 20]. The absence of low QRS voltages does not therefore preclude the diagnosis of amyloidosis, especially in patients with wild-type ATTR in whom mild left ventricular hypertrophy or left bundle branch block can be found in up to 30 % of patients. Additionally, a significant percentage of older adults with CA have pacemakers implanted to address conduction disease, making the electrocardiogram uninterpretable with regard to low voltage.

The true electrocardiographical hallmark of CA is the disproportion between left ventricular wall thickness and QRS voltages. This relationship can be expressed in a relatively complex way, with the formula published by Caroll et al. [21], or in a rougher but equally or even more efficient manner with the left ventricular wall thickness/total QRS voltage ratio [22].

Another frequent pitfall generated by the standard ECG is an initial incorrect diagnosis of coronary heart disease due to ST/T wave abnormalities and pseudo-infarction patterns. In fact, recent data suggest that pseudo-infarcts are more common (present in up to 70 % of patients with CA) than a low-voltage pattern [20].

Echocardiography

CA is one of the cardiomyopathies with a hypertrophic phenotype and is frequently misdiagnosed as sarcomeric hypertrophic cardiomyopathy [12, 15, 18]. Even though CA is usually considered a restrictive cardiomyopathy, an overt restrictive pathophysiology is uncommon and a restrictive trans-mitral Doppler filling pattern is not necessarily present and is not required for diagnosis [19].

Left ventricular function is rarely normal in CA despite a normal or near-normal left ventricular ejection fraction. Myocardial velocities and longitudinal deformation index offer the opportunity to overcome this pitfall [23]. Similarly, a novel imaging measure, the myocardial contraction fraction (MCF) which is the ratio of stroke volume to myocardial volume, is frequently abnormal in patients with CA despite a preserved EF [24].

While an initial reading of the echocardiogram highlights the hypertrophic phenotype, a more thorough analysis can expose the infiltrative disease hidden beneath. A partial list of red flags includes:

- increased thickness of A–V valves
- increased thickness of interatrial septum
- increased thickness of the right ventricle with depressed longitudinal function
- abnormal myocardial reflectiveness
- abnormal ventricular strain and strain rate (typically with apical sparing).

There is also the possibility of a paradoxical pitfall, in which the physician, having reached the diagnosis of CA, neglects other coexistent heart diseases. This risk is highest in elderly patients with AL or wild-type ATTR and hypertensive heart disease, coronary heart disease or degenerative aortic stenosis. This last possibility should be considered, especially in patients with low flow–low gradient aortic stenosis in whom amyloid infiltration could be the cause of impaired myocardial function.

Cardiac magnetic resonance

Magnetic resonance is currently considered the reference imaging technique for the diagnosis of AC due to accuracy of the morphological analysis (quantitative and qualitative) combined with myocardial substrate analysis offered by the gadolinium distribution profile [25–27]. It should, however, be kept in mind that:

- Late Gd accumulation is simply an expression of interstitial expansion, not a marker of amyloid infiltration and can be as frequent in storage diseases (Anderson–Fabry and Danon disease) and sarcomeric hypertrophic cardiomyopathy.
- Even though early studies showed a pattern of subendocardial late Gd accumulation, it is currently clear that the pattern of late Gd enhancement is highly variable [27] and the subendocardial pattern is not a prerequisite for the diagnosis.

The main red flag offered by magnetic resonance is the peculiar kinetics of Gd that can be assessed with dedicated T1 mapping sequences and equilibrium techniques [26, 28].

Scintigraphy

Scintigraphy with bone-seeking tracers (mainly DPD Tc in Europe and PYP Tc in US) is becoming the most popular nuclear medicine technique in the evaluation of amyloidosis [4, 29, 30]. It must, however, be kept in mind that myocardial uptake is strictly dependent on aetiology: absent or mild in AL, present in ATTR and variable in other rarer genetic forms [4]. A strong myocardial tracer uptake is highly sensitive for ATTR CA (both hereditary and wild type). Furthermore, specificity in relation to sarcomeric hypertrophic cardiomyopathy has also been shown to be high [31].

There are, however, potential pitfalls since a negative scintigraphy does, therefore, not rule out a diagnosis of (AL) CA and mild myocardial tracer uptake does not allow a differential diagnosis between ATTR and AL.

Histology

Despite the advances of non-invasive imaging techniques, histology remains the gold standard for the diagnosis of amyloidosis. In fact, a definite diagnosis requires both tissue biopsy proof of Congo red staining and verification of the protein subunit associated with amyloid. When interpreting the result of Congo red staining, one must consider that the intensity of apple green bi-refringency is partly determined by amyloid fibril composition (mixed full-length TTR and fragmented TTR have been associated with weak staining) [32].

Although it is a systemic disease, not all tissues have the same probability of demonstrating amyloid infiltration by histological examination. In a recent series of 131 patients with CA and a positive endomyocardial biopsy, only 73 % showed amyloid infiltration on non-cardiac tissue sampling [33]. Predictive accuracy of non-cardiac tissue is even worse for ATTR. In particular, periumbelical fat biopsy, when considered alone, is a source of misdiagnosis, especially in patients with wild-type ATTR where sensitivity is rarely higher than 50 % [2, 33].

The ultimate goal of a biopsy, in addition to documenting amyloid infiltration, is also to provide a definite aetiological classification. Immunohistochemistry is currently widely used to classify the form of amyloidosis but has major limitations, so that laser capture mass spectroscopic analysis of amyloid-laden tissue remains the gold standard (albeit single cases with uncertain results have been reported). The most frequent source of pitfalls related to immunohistochemistry is the coexistence of positivity for more than one type of antisera, typically those for TTR and lambda or kappa chains [2]. This is not the expression of multiple precursor amyloidogenic proteins but rather the result of antibody binding to circulating proteins present in the pathological specimen. In a recent series from the Mayo Clinic, 8/15 patients with monoclonal gammopathy showed strong TTR staining in the histological samples and mass spectrometry demonstrated light-chain amyloid in five of these eight patients [34]. The greatest risk of misclassification occurs in the patient with MGUS and multiple immunohistochemical positivity.

Conclusions

CA is a challenging and stimulating disease, in which the entire diagnostic pathway is riddled with pitfalls. The awareness of this condition is the most important prerequisite for the management of this risk. The experienced physician is aware of a series of caveats that are summarised in Table 3. Another important cultural aspect to keep in mind is that the many available laboratory tests and imaging techniques should be considered complementary rather than separate or as alternatives. In other terms, the question is not which is the "best" exam? But which is most useful and appropriate for each step of the diagnostic and therapeutic pathway. Table 4 summarises the diagnostic and decisional content of the main techniques in different phases of the diagnostic and therapeutic process.

A high preliminary suspicion for CA, a systematic approach to the evaluation of the presence and type of CA

Table 3 Caveats and pearls in cardiac amyloidosis

- A definite diagnosis of cardiac amyloidosis requires not only tissue biopsy proof of amyloidotic infiltration but also the identification of the precursor protein causing amyloid (since treatment strictly depends upon aetiology)
- A high index of suspicion is mandatory for the recognition of CA in the clinical arena (e.g. if you don't think of it, you won't diagnose it!)
- Cardiac amyloid should be suspected in any patient with heart failure, unexplained increased LV wall thickness and non-dilated LV
- In a patient with an initial diagnosis of HCM, look for the infiltrative phenotype hidden beneath the hypertrophic one!
- A distinctive sign of CA is the abnormal ratio between LV thickness and QRS voltages rather than low QRS voltages, alone. The absence of low QRS voltages does not rule out a CA if the context is otherwise fitting and up to 20 % of subjects with CA can have electrocardiographical evidence of LV hypertrophy
- In an elderly man with unexplained concentric LV hypertrophy, especially in the absence of hypertension, always consider the possibility of wild-type TTR CA!
- AC in an elderly patient with monoclonal gammopathy is not necessarily related to AL: consider the possibility of wild-type TTR + MGUS
- Longitudinal LV function can be severely depressed despite a normal LV ejection fraction and the myocardial contraction fraction are often low suggesting reduced global myocardial shortening
- Myocardial deformation is reduced in AC, but the apex is generally spared
- In CA, LGE distribution at MRI is heterogeneous: subendocardial LGE is not the only diagnostic pattern and the absence of LGE does not exclude CA
- Bilateral carpal tunnel syndrome in a man with HCM-like phenotype on echo is highly suggestive of TTR-related CA

CA cardiac amyloidosis, *LV* left ventricle, *HCM* hypertrophic cardiomyopathy, *MRI* cardiac magnetic resonance, *MGUS* monoclonal gammopathy of uncertain significance, *LGE* late Gd enhancement

Table 4 Usefulness of main tests in diagnosis and management of cardiac amyloidosis

Work-up stage	Echocardiogram	Magnetic resonance	Bone tracer scintigraphy	NT-proBNP and troponins
Suspicion	+++	++	+ (ATTR)	+
Definite diagnosis	+	++	+++ (ATTR)	–
Aetiological diagnosis	–	+?	+++	–
Early diagnosis	+	?	++ (ATTR)	+?
Functional evaluation	+++	++	+ (MIBG)	–
Prognostic stratification	++	+	+	+++
Amyloidotic burden	–	++ ?	+?	–
Response to therapy	±	?	?	+++ (AL)

MIBG metaiodobenzylguanidine

and the reliance on the expertise of multiple specialists are essential to ensure an early and accurate diagnosis of the "great pretender", CA.

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