

Left ventricular hypertrophy: diagnostic pitfalls

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Summary

Isolated left ventricular hypertrophy, in the absence of hypertension or aortic stenosis, is commonly attributed to hypertrophic cardiomyopathy (HCM). According to the clinical setting, however, other differential diagnoses should be considered. The diagnosis of cardiac amyloidosis may be very challenging especially when the clinician is confronted with various aspects typical of both pathologies.

The work-up of this case shows how non-invasive cardiac investigations are sometimes not sufficiently conclusive for distinguishing between the two pathologies, and that only endomyocardial

biopsy (EMB) can confirm cardiac involvement secondary to systemic amyloidosis.

The prognostic and therapeutic differences between the two diseases, as well as the contextual aspects of the case in point – namely a case of multiorgan failure – serve as an example of how a definitive diagnosis can be attained by means of a multidisciplinary approach in order to reach a definitive treatment plan.

Key words: hypertrophic cardiomyopathy, cardiac amyloidosis, endo-myocardial biopsy

Introduction

Isolated left ventricular hypertrophy in the absence of systemic arterial hypertension or aortic stenosis is commonly attributed to a hypertrophic cardiomyopathy (HCM), with or without dynamic obstruction. However, according to the clinical setting, other differential diagnoses should be excluded. In all dubious cases, the clinical presentation, the ECG and other diagnostic tools must be

brought together by the physician to establish the most probable diagnosis of myocardial thickening [1–3].

Cardiac amyloidosis is one of the reported differential diagnoses of left ventricular hypertrophy [4, 5] characterised by a poor prognostic outcome [6, 7].

Amyloidosis is differentiated into systemic and

Table 1
Characteristics of the systemic amyloidoses.*

| Type | fibril composition | precursor protein | clinical features | Laboratory studies for diagnosis |
|----------------------|---|--|---|--|
| AL (primary) | monoclonal immuno-globulin light chains | λ or κ light chains (ration of λ to κ 3:1) | cardiomyopathy, hepatomegaly, proteinuria, macroglossia, orthostasis, autonomic and peripheral neuropathy, ecchymoses | immunofixation electrophoresis of urine and serum, bone marrow biopsy with immuno-histochemical staining for λ and κ light chains |
| AA (secondary) | amyloid A protein | amyloid A protein | underlying inflammatory disorder, hepato-splenomegaly, proteinuria, renal insufficiency, orthostasis | elevated concentrations of serum amyloid A protein, immuno-histochemical staining of tissue specimen for AA protein |
| ATTR (familial) | transthyretin | abnormal transthyretin (>50 identified) | midlife onset of peripheral and autonomic neuropathy, cardiomyopathy, vitreous opacities | Serum isoelectric focusing for abnormal transthyretin or DNA-based test for mutant transthyretin gene |
| Other familial types | | | | genetic studies at special centers |
| AApoA-I | apolipoprotein A-I | apo A-I | polyneuropathy, nephropathy | |
| AGel | gelsolin | gelsolin | lattice dystrophy of cornea, corneal neuropathy | |

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*Modified from: Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med 1997;337:898–909

localised forms. Systemic amyloidosis is further sub-grouped into the hereditary familial form (eg, mutant transthyretin), the acquired form (AA), and the most frequent form: the light chain (AL) amyloidosis (Table 1) [2].

Treatment for amyloidosis can be symptomatic, directed at the affected organ, or more rationally directed at reducing the production of the abnormal proteins with different kinds of strategies (eg, intensive chemotherapy combined with autologous stem cell transplantation) [2].

Amyloidosis is usually a slowly progressive disease and its prognosis varies according to the different types of amyloid proteins and according to the entity of the involved organs. Survival ranges

from many years for the familial forms, to 1–2 years for the AL amyloidosis [2].

Furthermore, once cardiac involvement is diagnosed, there are usually important consequences, from a therapeutic as well as from a prognostic point of view [6, 8].

We present a case where obstructive left ventricular hypertrophy was identified on the basis of the clinical presentation, the ECG and the echocardiographic findings, but where the definitive diagnosis of cardiac involvement secondary to a systemic amyloidosis was only possible with the results of the endo-myocardial biopsies (EMBs). This finding determined the final therapeutic approach to the patient.

Case report

A 52-year-old white woman with liver cirrhosis due to alcohol abuse was evaluated for a liver transplantation, because of documented alcohol abstinence for more than 1 year.

The clinical cardiac evaluation showed an asymptomatic patient, able to climb 3 flights of stairs without dys-

pnoea, with normal arterial blood pressure, no cardiac murmurs or pulmonary rales. There was mild peripheral oedema attributed to the concomitant hypoalbuminaemia, sodium retention and hepatic cirrhosis. Finally, the patient's history did not reveal orthopnoea, syncope or chest pain.

The ECG showed a regular sinus rhythm, an atrioventricular conduction delay of 200 msec, an amputated R wave on the right precordial leads, with moderate diffuse low voltage (Figure 1) attributed to significant concomitant ascites and third space fluid.

The echocardiogram showed moderate thickening of the left ventricular walls (interventricular septum: 14 mm) with a supra-normal systolic function secondary to a hyper-dynamic state, and a moderate sub-aortic dynamic intraventricular end-systolic gradient (30 mm Hg at rest, 60 mm Hg at Valsalva manoeuvre) with a systolic anterior motion (SAM) of the anterior mitral leaflet generating a moderate mitral regurgitation. A thickening of the aortic and mitral valve and a mitral annulus calcification were also observed, without pericardial effusion (Figure 2). No diastolic dysfunction was detected with an E < A pattern of the mitral flow, considered normal for the age of the patient.

The final cardiological diagnosis reached was that of a hypertrophic cardiomyopathy with a moderate dynamic intracavitary obstruction in an asymptomatic patient.

Mildly impaired renal function (creatinine clearance: 58 ml/min – normal range: 75–115 ml/min) with proteinuria (2.5 g/24 h) was further investigated with serum and urine protein-electrophoresis, which showed a biclonal gammopathy (IgA Kappa and IgG lambda) attributable to a biclonal gammopathy of unknown significance (BGUS), confirmed by bone marrow biopsy (15% of plasma cells: Lambda 3:1 Kappa).

The histological examination of the kidney biopsy permitted the final diagnosis of a systemic amyloidosis type AL secondary to a BGUS to be made.

Due to a rapid deterioration of renal function the patient was considered for double organ transplantation (kidney/liver).

Because cardiac involvement secondary to systemic amyloidosis is often observed [2], we performed a cardiac catheterisation which excluded a restrictive haemodynamic pattern compatible with an infiltrative cardiac disease. An endo-myocardial biopsy (EMB) of the right ventricle [9–11] was complicated by a perforation with mild pericardial effusion treated conservatively, and a transient, spontaneously remitting sinus arrest with right bundle branch block and junctional escape rhythm.

Figure 1

12 lead ECG (10 mm/mV; 25 mm/sec) showing a regular sinus rhythm, an atrioventricular conduction delay of 200 msec, an amputated R wave on the right precordial leads, with a diffuse low voltage (<0,5 mV).

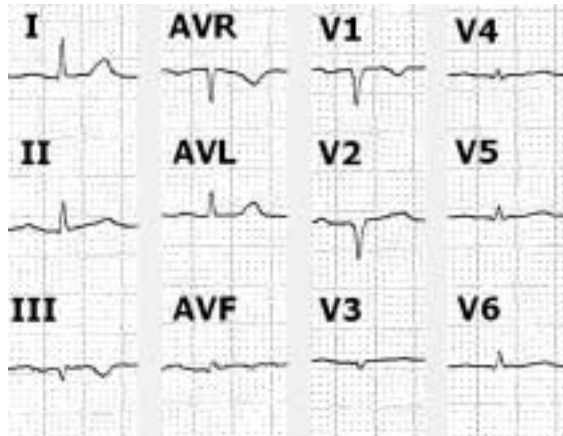


Figure 2

Apical four chamber view of a two dimensional echocardiogram, showing a moderate thickening of the left ventricular walls (interventricular septum 14 mm: arrowhead), with a mild granular sparkling only in the right ventricular portion of the septum (I), and a systolic anterior movement of the cord of the postero-medial papillary muscle of the anterior mitral leaflet (SAM: white arrow). LV = left ventricle LA = left atrium black/white arrow = mitral annulus calcification

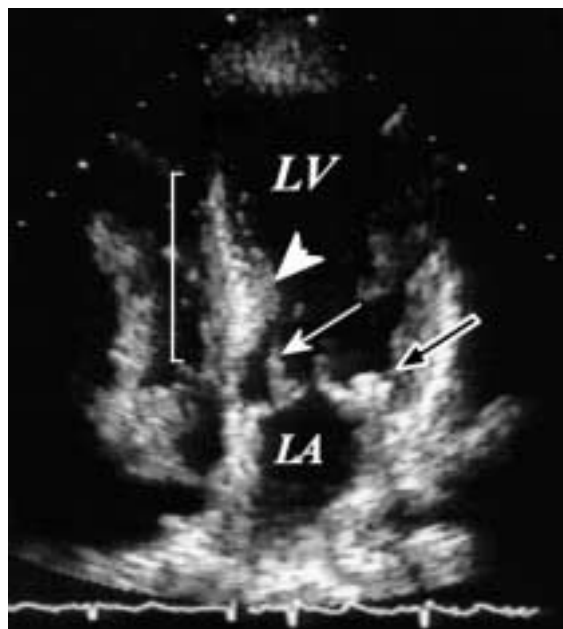
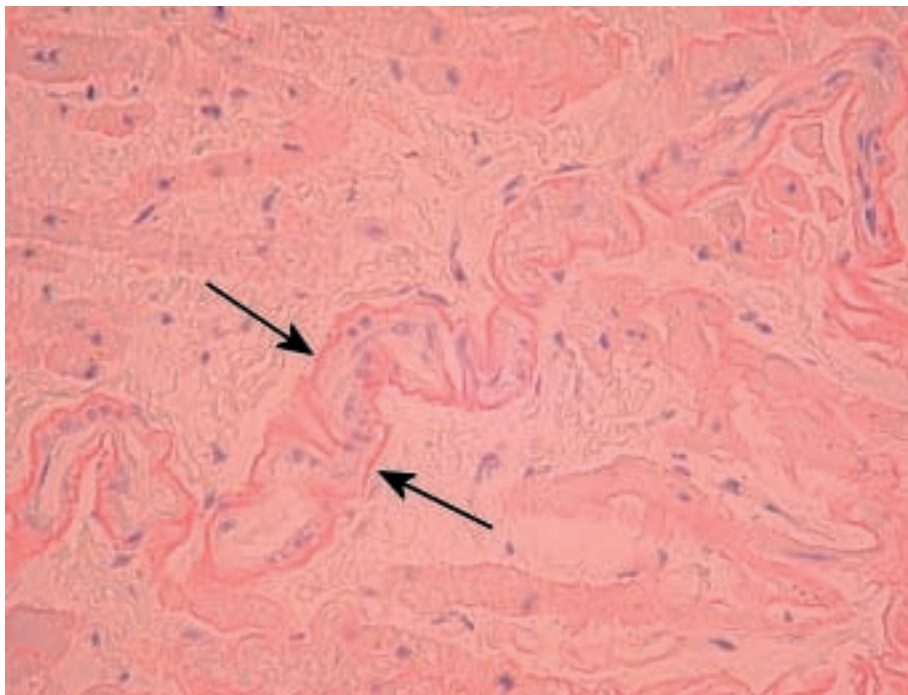


Figure 3

Endo-myocardial biopsy showing a homogenous acellular eosinophilic infiltration, positive for Congo red staining, confirming cardiac infiltration in systemic amyloidosis, especially in the perivascular contour (arrows).



Considering the overall clinical history, the marked fragility of the heart during biopsy, the thickening of the left ventricular walls and of the aortic valve, the moderate low voltage with a pseudo anterior old infarction image on the ECG, cardiac involvement secondary to the systemic

amyloidosis was suspected and eventually histologically confirmed (Figure 3). Following the diagnosis of systemic amyloidosis with cardiac involvement, with known poor outcome [2, 3], the planned kidney/liver transplantation was deemed to be contraindicated.

Discussion

This case confirms that the distinction between a HCM and a cardiac amyloidosis with left ventricular hypertrophy is not always easy, especially when the clinician is confronted with many aspects, typical of both pathologies [4, 5].

In fact, in our case the echocardiographic presence of a mild granular sparkling only in the right ventricular portion of the septum, not pathognomonic [12] but often associated with amyloid infiltration in the myocardium, the asymmetrical septal "hypertrophy" with a SAM, without interatrial septum thickening or restrictive pattern of the mitral flow, was more suggestive for a HCM than a cardiac amyloidosis [1].

Therefore, the diagnosis of cardiac amyloidosis using the mentioned non-invasive cardiac investigations remained speculative with a positive predictive value of 79% [11], and could only be definitively confirmed by histology (3/3 positive EMBs, Figure 3).

In similar cases, with a moderate-to-high clinical suspicion of cardiac involvement of through systemic amyloidosis the EMB remains a very powerful tool to confirm the presence of amyloid deposits in the myocardium with a sensitivity of almost 100% [9, 10]. Therefore, even if not free from complications (1.1% arrhythmias, 1% conduction abnormalities, 0.5–1.2% perforations,

0.4% deaths) [13], we suggest performing EMB in all dubious situations, where a correct cardiac diagnosis could have relevant clinical, therapeutic and especially prognostic consequences.

Concerning the cardiac final diagnosis, even with documented cardiac amyloidosis, the concomitance of a second cardiac disorder (ie, HCM) is difficult to rule out definitively. In fact, a combined cardiomyopathy is possible, especially, when many aspects typical of both pathologies are present [14, 15], and even in such a context this rare double cardiomyopathy can be diagnosed with certainty only post-mortem [15].

At a 12-month follow up examination, the patient was still asymptomatic from a cardiological point of view, however performing haemodialysis for her renal insufficiency.

Contrary to what is frequently observed in patients where cardiac symptoms are predominant, this case suggests that an early diagnosis of a cardiac amyloidosis is not always related to a poor outcome (ie, 12 months survival from the diagnosis or 6 months from the first cardiac symptoms) [6], because under an adequate cardiovascular treatment, this systemic disease can also progress very slowly [16].

To this day, current opinion supports a conservative attitude, in patients with documented

secondary amyloid involvement of at least two major organs (in our case kidney/heart) [8, 17].

In conclusion, we would like to emphasise that left ventricular hypertrophy of unknown aetiology should be thoroughly explored (ie, EMB) when an infiltrative cardiac disease is suspected and when an aggressive treatment strategy is planned.

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