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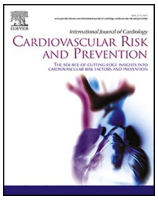

Cardiac amyloidosis red flags: What all the cardiologist have to know

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ABSTRACT

Cardiac amyloidosis is becoming increasingly important among cardiologist and an early diagnosis is very important. Amyloidosis is a systemic disease and many cardiac and extracardiac elements (red flags) should raise the suspicion of the disease. Electrocardiographic and imaging techniques (such as echocardiography, cardiac magnetic resonance and scintigraphy) are useful tools to make a diagnosis together with the presence of orthopedic issues, peripheral neuropathy or plasma cell dyscrasia. Cardiac amyloidosis is also often associated with valvular disorder, heart failure or cardiomyopathy. Red flags are crucial to raise suspicion and reach an early diagnosis, in order to start a targeted treatment strategy that could change the patient's outcome. Indeed, in the last years four new drugs were approved to treat transthyretin amyloidosis.

1. Introduction

Systemic amyloidosis involves amyloid fibril deposits in various organs, leading to their progressive dysfunction. These insoluble fibrils, composed of low molecular weight protein subunits, undergo conformational changes causing auto-aggregation. Cardiac amyloidosis involvement results in infiltrative cardiomyopathy with a hypertrophic phenotype and determine a significantly prognosis worsening. Early diagnosis is crucial for increase treatment effectiveness and modify the disease's natural history.

2. Epidemiology

Transthyretin (TTR) and immunoglobulin light chains (AL) account for about 98 % of cardiac amyloidosis cases. TTR amyloidosis is divided into wild type (wtTTR), with normal transthyretin deposition, and hereditary TTR (hTTR) due to over 130 amyloidogenic mutations. Cardiac involvement is predominant in wtTTR, while hTTR shows varied phenotypes (polyneuropathy/cardiomyopathy) depending on the mutation. AL amyloidosis, related to plasma cell dyscrasias producing monoclonal immunoglobulin light chains, often presents with a systemic involvement, affecting kidneys, liver, nerves, and heart [1].

Cardiac amyloidosis, once rare, is now increasingly diagnosed due to better detection and awareness, especially among cardiologists, influenced by the availability of effective treatments. Conditions like aortic stenosis, heart failure, or hypertrophic cardiomyopathy often mask undiagnosed amyloidosis; for instance, wtTTR was found in 13 % of heart failure patients with preserved ejection fraction when amyloidosis was actively screened.

3. ATTR amyloidosis red flags

Given the systemic nature of amyloidosis, red flags for the disease include both cardiac and extracardiac findings (Table 1) [2]. Cardiac red flags are heart failure symptoms (often with preserved ejection fraction), abnormal electrocardiogram (ECG), elevated troponin and NT-proBNP, and specific findings in echocardiograms and cardiac magnetic resonance imaging (CMR). ECG changes are generally non-specific, showing pseudo-infarction patterns, poor R-progression, delays in atrioventricular and interventricular conductionm and low voltage which contrasts with the increased thickness seen in echocardiograms (mass/voltage discrepancy).

The more typical echocardiographic red flag is, at strain analysis, a longitudinal dysfunction with preserved strain in the left ventricular apex (also called 'apical sparing'). Additional echocardiographic red flags include valvular disorders such as paradoxical low-flow low-gradient aortic stenosis (typically in wtTTR) and valve thickening with different insufficiency degrees. Among findings from second-level examinations, CMR often displays a typical pattern of late gadolinium enhancement distribution (diffuse subendocardial but also transmural)

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Table 1
Red flag for amyloidosis cardiac involvement.

Cardiac manifestation	
Clinical	Heart failure symptoms especially due to right ventricle involment. Family history of heart failure in hereditary form. Fatigue. Low normal BP in patients with history of hypertension. Intolerance to beta-blockers or ACE-I. Orthostatic hypotension.
Laboratories	Elevated B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide. Persistent low-level troponin elevation without significant variation during follow-up.
Electrical	Conduction system disorder: AV conduction disorder, LBBB/RBBB. Atrial fibrillation. Pseudonecrosis Q waves. Mass/voltage discrepancy with low QRS voltages.
Imaging	Thickening of the septum, posterior wall or RV wall. Valve thickening in advanced disease state. Preserved or mildly reduced ejection fraction. Small pericardial effusion. Pleural effusion. Grade 2 or worse diastolic dysfunction. Enlarged atria. Abnormal longitudinal stain with apical sparing pattern. Paradoxical low flow-low gradient aortic stenosis. Cardiac uptake with bone tracers (scintigraphy with technetium-based compounds). Diffuse subendocardial or transmural late gadolinium enhancement on cardiac magnetic resonance imaging. Increased extracellular volume fraction.
Extracardiac manifestation	
Musculoskeletal	History of bilateral carpal tunnel syndrome. Popeye sign due to spontaneous biceps tendon rupture (only in ATTR amyloidosis). Lumbar or cervical spinal stenosis (only in ATTR amyloidosis). History of knee or hip replacement. Trigger finger.
Neurologic	Peripheral neuropathy: painful neuropathy in hands and feet, muscle weakness. Autonomic neuropathy: symptoms due to gastrointestinal dysmotility, erectile dysfunction, orthostatic hypotension.
Renal	Nephrotic syndrome with significant proteinuria (more common in AL amyloidosis).
Specific sign	Macroglossia or submandibular gland enlargement from soft tissue involvement (only in AL amyloidosis). Periorbital purpura due to capillary fragility and acquired Factor X deficiency (only in AL amyloidosis).
Laboratories	Abnormal serum kappa/lamda free light chain or serum/urine immunofixation (only in AL amyloidosis).

Abbreviations: BP = Blood Pressure; LBBB = Left Bundle Branch Block; RBBB= Right Bundle Branch Block; RV = Right Ventricle; ATTR = Amyloid TransThyRetin; AL = Amyloid Light chain.

and typical kinetics (with accelerated contrast wash-out or increase T1 mapping and calculated extra cellular volume). Additionally, bone scintigraphy detecting radiotracer uptake can suggest, with high specificity and sensitivity, a cardiac TTR amyloidosis. Extracardiac red flags include musculoskeletal, gastrointestinal and neurological items. Carpal tunnel syndrome is particularly common, and often bilateral, in wtTTR patients and can precede heart failure from 7 to 10 years. Other orthopedic issues include lumbar spinal stenosis, biceps tendon rupture and early need for knee and hip intervention. Peripheral polineuropathy, a key symptom in hTTR, can also occur in wtTTR, usually presenting as symmetric and sensory. A notable characteristic in TTR patients is the intolerance to antihypertensive or heart failure medications, often because of orthostatic hypotension. For the same reason, TTR can be suspected in patients who doesn't need any more antihypertensive medication during the aging process.

4. Treatment of TTR cardiac involvement

There are currently two different therapeutic strategies effective for TTR-induced cardiac amyloidosis treatment: (i) the 'silencing' of TTR synthesis and expression and (ii) the stabilization of TTR proteins with the aim of limiting their degradation.

Patisiran, inotersen and vutrisiran are gene silencer approved by the American and European regulatory agencies when there is a neurological involvement despite they demonstrate positive results also on cardiac amyloidosis. Patisiran is a small interfering RNA administered intravenously every 3 weeks that in 360 TTR patients (APOLLO-B phase 3 randomized trial) demonstrate a significant clinical benefit in functional capacity (6-Minute Walking Test – 6-MWT), health status, and quality of life in comparison with placebo over a 12 months period; a NT pro BNP levels reduction was also highlighted [3]. Inotersen is an antisense oligonucleotide inhibitor of transthyretin mRNA administered weekly by subcutaneous injection. In patients with TTR cardiomyopathy it improves 6-MWT results and global systolic longitudinal strain [4]. Vutrisiran is an RNA interference therapy; it has demonstrated a significant improvement in neuropathy impairment and quality of life and a trend towards improvement of echocardiographic parameters.

The other approach to the treatment of TTR amyloidosis is to stabilize the tetrameric TTR protein complex, thereby preventing its dissociation into amyloidogenic TTR monomers and oligomers. Tafamadis is an orally bioavailable agent that acts by binding, with high affinity and selectivity, to thyroxine sites on both wild-type and variant TTR. It has been investigated in the ATTR-ACT study (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) [5] that evaluated 441 patients (106 hTTR and 335 wtTTR) with Tafamidis 80 mg vs 20 mg vs placebo. In a pooled analysis, both doses of Tafamidis were associated with a reduction in all-cause mortality (29.5 % vs 42.9 %, HR 0.70; CI 0.51–0.96) and a 32 % reduction in hospitalizations for cardiovascular causes in patients with NYHA Class I and II. Among the secondary endpoints a lower rate of functional capacity (6-MWT distance) and of quality of life decline was observed.

There was a higher rate of cardiovascular-related hospitalizations in patients with NYHA class III symptoms on treatment, which has been postulated to be due to longer survival in a more critical stage of disease. However, a report published in 2022 showed an improved 5-year follow-up survival among these patients when treated with Tafamidis compared to placebo. Analysis of data from the 'long-term extension' study of patients from the ATTR-ACT study demonstrated that the reduction in mortality can be prolonged in the long term up to a follow-up of 58 months and that the survival was better in the group treated early with Tafamidis, suggesting the importance of early administration to prevent TTR fibril formation.

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Declaration of competing interest

The authors declare they have no conflict of interest.

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