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Diagnostic approach to light-chain cardiac amyloidosis and its differential diagnosis

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Abstract
Cardiac amyloidosis is a rare and often-misdiagnosed disorder. Among other forms of deposits affecting the heart, immunoglobulin-derived light-chain amyloidosis (AL amyloidosis) is the most serious form of the disease. Delay in diagnosis and treatment may have a major impact on the prognosis and outcomes of patients. This review focuses on the presentation of the disorder and current novel approaches to the diagnosis of cardiac involvement in AL amyloidosis.

Keywords:
cardiac AL amyloidosis, echocardiography, endomyocardial biopsy

Introduction

Amyloidosis is a rare disorder caused by extracellular deposition of insoluble amyloid fibrils that disrupt the architecture of the affected tissues and cause organ dysfunction. The clinical phenotype depends on the involvement of particular organs and the type of deposition. The frequency of cardiac involvement varies among the various types of amyloidoses. Classification of amyloidoses is based on the type of amyloid protein and its identity. More than 30 types of proteins are known to cause amyloid deposition. The three most common forms of amyloidosis are light-chain amyloidosis (AL), secondary amyloidosis (AA), and transthyretin-related amyloidosis (ATTR). In AL amyloidosis, deposits are composed of monoclonal immunoglobulin (Ig) kappa or lambda light chains. The estimated prevalence in the UK is 3-5/year per 1,000,000 inhabitants [1]. Approximately 250 new patients with AL amyloidosis are detected per year in Poland [2]. Involvement of the heart in AL amyloidosis occurs in 50% of cases, whereas isolated cardiac AL amyloidosis concerns < 5% of patients [3]. Cardiac amyloidosis has the worst prognosis on any involved organ, and AL amyloidosis is the most serious form of the disease [4]. Intrinsic properties of the amyloid deposition, host immune response, and the amyloid nanoenvironment play key roles in the cardiotoxicity [5]. Advanced cardiac involvement is the strongest predictor of poor patient outcome, and median survival for untreated patients with congestive heart failure in course of AL is < 6 months [6]. Therefore, early recognition of cardiac AL amyloidosis with implementation of novel therapeutic strategies is crucial to help with better clinical outcomes of patients [7]. Recently published data show that administration of modern therapies leads to prolonged remission and extended life expectancy.

Clinical features

Establishing a diagnosis of systemic amyloidosis is complicated because of the variety of nonspecific clinical features of the disease depending on the type and number of organs affected [2]. The most common clinical signs of AL amyloidosis include nephrotic syndrome (70%), restrictive cardiomyopathy (60%), peripheral neuropathy (20%), hepatomegaly with elevated levels of liver enzymes (70%), hypotension (30%), macroglossia, muscle involvement, skin manifestations, and bleeding diathesis [8]. Patients complain of fatigue, loss of body weight, and carpal tunnel syndrome. Macroglossia, dysphagia, speech impairment, nail dystrophy, easy bruising, and peripheral purpura (called raccoon or panda eyes) are pathognomonic stigmata of disease.

Cardiac involvement manifestation

Cardiac manifestation occurs in one-third to one-half of patients suffering from AL amyloidosis [9]. Patients with initially nonspecific cardiac symptoms are undiagnosed until development of severe heart failure [10]. Isolated primary cardiac amyloidosis is a very rare manifestation of AL amyloidosis (< 5% of patients) and is associated with a poor prognosis [3]. The classical presentation of AL cardiomyopathy is a rapid progression of symptoms of diastolic heart failure, which may result in many serious heart consequences such as arrhythmias, syncope, ischemic heart disease, and intracardiac thrombus formation. Atrial fibrillation is seen in 9% of patients [11]. Hypotension is common in AL cardiac amyloidosis [12]. Progressive heart failure and electromechanical dissociation are the most common causes of death in patients with cardiac amyloidosis [13].

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Diagnostic approach

General approach

Clinical signs and results of noninvasive diagnostic investigation facilitate establishment of a diagnosis of amyloidosis; they, however, do not differentiate the subtypes of the disease. Undoubtedly, identification of the amyloid source is crucial for the implementation of an appropriate therapy and to avoid severe therapeutic errors. According to updated noninvasive consensus diagnostic criteria for AL amyloidosis, cardiac involvement is defined as mean left ventricular (LV) wall thickness on echocardiography > 12 mm with no other causes found and the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) level > 39 pmol/l in the absence of renal failure or atrial fibrillation [14]. The diagnosis of suspected AL cardiac amyloidosis requires cooperation between hematologists and cardiologists (Fig. 1) [15].

Histological findings

Routine histopathologic diagnosis of amyloidosis requires identification of the amyloid, based on tissue biopsy. The amyloid protein binds Congo red dye or thioflavin T, producing apple green birefringence under polarized light [16]. Biopsy of easily accessible sites, such as abdominal fat, minor salivary glands, the rectum, or gingiva can spare patients endomyocardial biopsy (EMB). Fine-needle aspiration of abdominal fat is positive in 70% of patients with AL amyloidosis [17]. Histopathological examination is indispensable; however, it is unable to differentiate between amyloid subtypes [18]. Confirmation of AL amyloidosis requires the identification of kappa or lambda chains in amyloid deposits. Determination of the amyloid subtype is performed using the following methods: immunohistochemical staining, immunoelectron microscopy (IEM), and laser microdissection with mass spectrometry. Although not widely available, proteomic evaluation of amyloid deposits by mass spectrometry allows for highly sensitive and specific results to determine the precise component of the amyloid deposits [4].

EMB may allow diagnosis of AL cardiac amyloidosis in cases where other tissue biopsies are not available. This is a gold standard diagnostic tool directly proving the presence of amyloid infiltration; however, it should be performed only in specialized centers by experienced operators [19]. EMB is an invasive procedure, with the risk of serious complications. During the procedure, heart catheterization is performed, enriching the operator information from

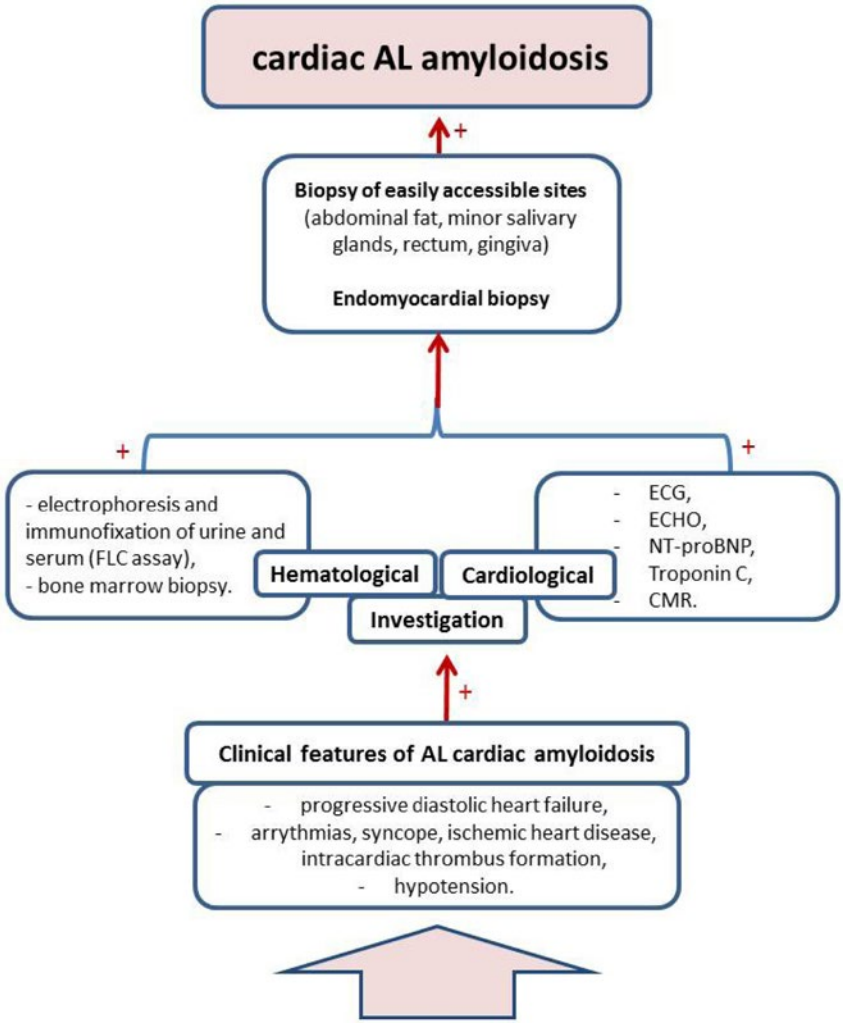

Fig. 1. Diagnostic algorithm for cardiac AL amyloidosis

hemodynamic measurements [4]. Right ventricular EMB is routinely performed; however, recently, LV EMB appears diagnostically more contributive [20, 21]. The sensitivity of cardiac biopsy varies depending on the phase of amyloid infiltration. In a group of patients with unexplained cardiomyopathy, EMB turned out to be more sensitive than initial clinical diagnosis (100% vs. 81%) in a subgroup of AL amyloidosis patients [22].

Hematological assessment

All patients with suspected AL amyloidosis should undergo hematological evaluation to determine the percentage of bone marrow plasma cells present and the presence of monoclonal protein to rule out concomitant multiple myeloma and other hematological disorders. Electrophoresis and immunofixation of serum and urine should be performed to display the presence of monoclonal (M) protein and abnormal serum free light chain (FLC) ratio in AL amyloidosis. Monoclonal IgG protein (35%), IgA protein (10%), IgM protein (5%), and IgD protein (1%), as well as free light chains (49%), can be found in AL amyloidosis patients [23]. Lambda light chains are present in 70%, kappa type in 25%, and the biclonal type in 5% of patients [24]. Typically, lambda chains prevail over kappa in the ratio of 3:1, which differs from multiple myeloma, in which this ratio is 2:3. Bone marrow biopsy in AL amyloidosis may reveal an increased percentage of plasma cells that may appear morphologically normal, with a median percentage of < 10% [25]. Immunoperoxidase staining or flow cytometric analysis of specimens of the involved bone marrow can demonstrate clonal excess of plasma clone cells. Bone marrow biopsy is 50% sensitive for detecting deposits of amyloid, but, performed with fat pad aspirate, can be up to 85% sensitive [26].

Cardiac biomarkers

Biomarker-based staging systems are crucial for patient stratification in clinical trials and to implement proper therapy regarding patients' suitability for high-dose chemotherapy and autologous stem cell transplantation. The expert community has stated that NT-proBNP is an analytically validated biomarker for use as a surrogate and end point for survival in cardiac AL amyloidosis patients. NT-proBNP is an indicator of cardiac response [27]. Long-term outcomes of patients with AL cardiac amyloidosis are more likely related to underlying clonal disorders; thus, the revised Mayo staging system for AL amyloidosis includes serum differences between involved and uninvolved light chains (FLC-diff) in the risk stratification of patients [28].

Noninvasive heart-imaging methods

Noninvasive heart-imaging methods play a key role in the diagnostic approach to cardiac AL amyloidosis; however, they cannot distinguish the subtype of amyloid infiltration.

Echocardiography

Echocardiography remains an essential diagnostic method providing assessment of the function and morphology of the heart. Standard echocardiography with tissue Doppler may reveal certain or all characteristics, but all are nonspecific features of cardiac amyloidosis. Classic abnormalities include concentric LV wall thickening, moderate-to-severe diastolic dysfunction, restrictive filling pattern, biatrial dilatation, pericardial and pleural effusions, as well as diffuse valvular and interatrial septal thickening [29]. Echocardiography reveals the "granular", "sparkling" appearance of ventricular thickened myocardium [30]. In amyloid cardiomyopathy, a restrictive pattern of LV filling with high filling pressures is considered pathognomonic and indicates increased ventricular stiffness occurring in the late stages of cardiac amyloidosis [31]. Left atrial dysfunction in the presence of the sinus rhythm is associated with an increased risk of thrombus formation [32] and a worse outcome. Myocardial strain imaging is a useful echocardiographic technique detecting systolic impairment with strain and strain rate and is more sensitive than the standard tissue Doppler [33]. Two-dimensional feature-tracking imaging (FTI) and speckle-tracking imaging are methods allowing myocardial motion analysis frame by frame throughout the cardiac cycle. The FTI technique helps to distinguish between LV thickening in cardiac amyloidosis and hypertrophic cardiomyopathy.

Cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) is sensitive in detecting amyloid cardiomyopathy and has excellent spatial resolution for tissue characterization. It provides imaging of the atrial structure, heart systolic function, and morphology of restrictive cardiomyopathy [34]. Late gadolinium enhancement (LGE), expansion of the extracellular volume (ECV), and abnormally prolonged T1 times (before or after contrast) are characteristic features visible on CMR in patients with amyloid cardiomyopathy. LGE reveals pathognomonic endocardial and myocardial wall enhancement, which is highly sensitive and specific for cardiac amyloidosis [35]. The prevalence of myocardial LGE can increase up to 97% and different LGE patterns can be observed, e.g., "patchy" [36]. Gadolinium uptake in cardiac amyloidosis is observed in the atria, which is rare in other cardiomyopathies [37]. Measurement of ECV indicates myocardial extracellular matrix expansion even in segments in which LGE cannot be seen [38]. CMR T1 mapping reveals a myocyte response to amyloid infiltration through measurement of the native (noncontrast) myocardial longitudinal relaxation time of tissue.

Electrocardiography

Abnormalities are found in 90% of patients with AL cardiac involvement on electrocardiography (ECG) [39]; however, this method is not sufficient to establish a diagnosis. Low voltage on ECG is a characteristic feature, present in 56% of patients [40]. Other classic findings include atrial fibrillation/flutter (20%), first-degree atrioventricular block (21%), nonspecific intraventricular conduction delays (16%), and second- or third-degree atrioventricular block (3%) [39]. Ventricular tachycardia (5%), left and right bundle branch block, and pseudoinfarct patterns (60%) can be also be observed [41].

Nuclear imaging

Several nuclear medicine imaging techniques have become available for the diagnosis and prognostic stratification of cardiac amyloidosis [42]. Bone scintigraphy using radiolabeled ^{99m}Tc-3,3-diphosphono-

1,2-propanodicarboxylic acid tracer is useful in differentiating between ATTR and AL cardiac amyloidoses, revealing a positive uptake in ATTR cardiac amyloidosis [43] and false-positive results in AL cardiac amyloidosis [44].

Differential diagnosis of cardiac AL amyloidosis

It is important to distinguish the subtypes of amyloidosis, monoclonal Ig deposition diseases (MIDDs), and various cardiologic causes of LV hypertrophy.

Based on the nature of the amyloid precursor protein, several forms of amyloidosis with distinct clinical features are recognized. The most common types of cardiac amyloidosis are presented in table I.

All amyloid deposits misfold to beta-pleated fibrillar configuration and demonstrate staining with Congo red and bind with thioflavin T; however, only direct examination of the amyloid deposits enables determination of the subtype of the disease. The echocardiographic appearance is almost indistinguishable between the subtypes of cardiac amyloidosis.

The MIDDs

The MIDDs are clonal plasma cell proliferative disorders, in which Ig light or heavy chain fragments form tissue deposits, which lead to organ dysfunction. In contrast to amyloid deposits, the MIDD tissue deposits are granular and do not stain positive with Congo red and thioflavin T. Table II shows the characteristic features of MIDD in comparison with amyloidosis.

Involvement of the heart in MIDD may mimic AL amyloidosis. The echocardiographic appearance is similar to that in cardiac amyloidosis. Heart failure and arrhythmias may occur.

Non-Q-wave heart infarction

Non-Q-wave heart infarction can be misdiagnosed in the presence of AL cardiac amyloidosis infiltrating small vessels in the myocardium [49]. Clinically, patients present angina-like chest pain. Troponin level elevation may represent ongoing myocyte necrosis and has been shown to be a negative prognostic factor [50].

LV hypertrophy

Various causes of LV hypertrophy, including hypertensive heart disease, hypertrophic cardiomyopathy, Fabry disease, mitochondrial cardiomyopathy, and other causes of restrictive cardiomyopathy such as infiltration with metastatic cancer [10], should also be taken into account. Hypertensive heart disease, hypertrophic cardiomyopathy, or Fabry disease with LV hypertrophy is associated with an increased or normal electrocardiogram voltage, unlike the low-voltage electrocardiogram observed in amyloid infiltration. Echocardiographic features such as valve thickening, thickened interatrial septum, and diffuse increase in echogenicity help to distinguish cardiac amyloidosis from other causes of restrictive cardiomyopathy and LV hypertrophy. Specific amyloidosis CMR findings, such as LGE, are not expected in other causes of LV hypertrophy and restrictive cardiomyopathy.

Table I. Most common subtypes of amyloidosis [4, 26, 45-47]

Cardiac amyloidosis	Pathophysiology	Average age at presentation	Frequency of cardiac involvement	Comments
AL Light chain amyloidosis	**Immunoglobulin light chain** Underlying plasma cell dyscrasia	> 50 years	50%	–
ATTR Hereditary amyloidosis	**Mutant transthyretin** Genetic mutations cause misfolding of hepatic-derived transthyretin into amyloid material	> 40 years	90%	Certain mutations can cause progressive cardiomyopathy, leading to heart failure [45]
SCA Senile cardiac amyloidosis	**Wild-type transthyretin** Age-related protein deposition	> 65 years	Almost 100%	Occurs most often in men [4]; manifests as congestive heart failure: in 91% involves atria [46]
AA Secondary amyloidosis	**Serum amyloid A** Chronic inflammatory conditions, malignancy leading to increased hepatic production of the acute phase reactant serum amyloid A	60-70 years	Rare	May occur in 20s-30s with severe inflammatory disease [4]; does not affect heart in clinically significant manner [47]

Table II. Characteristic features of plasma cell proliferative disorders forming tissue deposits [3, 48]

Feature	Monoclonal immunoglobulin deposition diseases (MIDDs)		Amyloidosis
Subtypes	90%	**Light chain deposition disease (LCDD)**	**AL amyloidosis**
	10%	**Light and heavy chain deposition disease (LHCDD)**	**AH amyloidosis** (heavy-chain amyloidosis)
		Heavy chain deposition disease (HCDD)	
Structure of deposits	**LCDD**: fragments of light chains; κ chains (68%), λ chains (32%); normal sized or short		**AL amyloidosis**: normal-sized or enlarged light chains (λ type – 75%, κ type – 25%)
	LHCDD: associated heavy chains		**AH amyloidosis**: short heavy chains
	HCDD: short (truncated) heavy chains		
Cardiac involvement	< 10%		**AL amyloidosis**: 50%

Summary

Diagnosis of cardiac AL amyloidosis should be considered in adult patients with unexplained heart failure and an echocardiogram showing increasing wall thickness with a nondilated LV cavity, especially in the absence of a history of hypertension.

Modern diagnostic techniques, particularly advanced echocardiography and cardiovascular magnetic resonance findings, are helpful in supporting the diagnosis of AL amyloidosis. Early identification and diagnosis of AL amyloidosis is important to provide timely medical therapy. Administration of modern therapies has not only halted the progression of the disease but has also led to prolonged remission and improvement of the outcomes.

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