

# Cardiac amyloidosis

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## Abstract

Amyloidosis is a family of disorders of the immune system in which one or more organs in the body accumulate amyloid. There are four different forms of amyloidosis: systemic amyloid light chain (AL) amyloidosis, amyloid A (AA) amyloidosis, hereditary, and senile amyloidosis. The abnormal proteins can be found as Bence-Jones proteins in urine mainly in patients with light chain (AL) amyloidosis. Cardiac amyloidosis is a myocardial disease characterized by extracellular amyloid infiltration throughout the heart and is an important cause of progressive heart failure (restrictive cardiomyopathy) with a wide spectrum of clinical manifestations. Typically, cardiac arrhythmias and diastolic heart failure occur, followed by sudden cardiac death in many cases. The diagnosis of cardiac amyloidosis is a combination of clinical, electrocardiographic and imaging methods, but definite diagnosis is based on endomyocardial biopsy. Prognosis of AL amyloidosis is poor and treatment is often a challenge, although a combination of high-dose chemotherapy, autologous stem cell transplantation and heart transplantation have shown survival benefits. Reactive AA amyloidosis may respond to anti-inflammatory and immunosuppressive drugs.

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## Background

Amyloidosis is a family of disorders of the immune system in which one or more organ systems in the body accumulate deposits of abnormal proteins [1]. The name “amyloidosis” was first used more than 100 years ago, yet only within the past 25 years have physicians understood the specific make-up and structure of amyloid protein. Amyloidosis represents a diverse group of diseases characterized by the common factor of deposition of twisted  $\beta$ -pleated sheet fibrils (amyloid) formed as a result of the misfolding of various proteins produced in several different pathological states [1].

The various forms of amyloidosis are classified by the composition of the amyloid fibril. The three major types of amyloidosis are different from each other. Amyloid light chain (AL) amyloidosis (also known as primary amyloidosis) is a plasma cell disorder that originates in the bone marrow. It is the most common

type of amyloidosis and occasionally occurs with multiple myeloma. The deposits in this type of the disease are made up of immunoglobulin light chain proteins, which may be deposited in any bodily tissues or organs. The disease results when enough amyloid protein builds up in one or more organs to cause the organ(s) to malfunction. The heart, kidneys, nervous system, and gastrointestinal tract are most often affected. **Secondary amyloidosis** is caused by a chronic infection or inflammatory disease such as rheumatoid arthritis, familial Mediterranean fever, osteomyelitis, or granulomatous ileitis. The deposits in this type of the disease are made up of a protein called the **amyloid A (AA) protein**. **Familial amyloidosis** is the only type of amyloidosis that is inherited. The deposits in this type are most commonly made up of the transthyretin protein, which is manufactured in the liver [1].

In elderly persons, cardiac amyloidosis is an important cause of progressive heart failure and refractory

arrhythmia of obscure origin [2]. The average survival time of amyloid heart disease after the onset of symptoms is less than three years. Clinically, amyloid heart disease may mimic constrictive pericarditis, coronary artery disease, valvular heart disease, and hypertrophic or congestive cardiomyopathy.

Cardiac amyloidosis belongs to the family of restrictive cardiomyopathies. Restrictive cardiomyopathy is characterized by abnormal diastolic function with either thickened or rigid ventricular walls leading to elevated filling pressures of the left- or right-sided cardiac chambers. The classification of restrictive cardiomyopathy is based on etiological and clinical findings. Primary forms are Löffler's endocarditis and endomyocardial fibrosis. To the secondary forms belong infiltrative diseases, storage diseases, and post-radiation disease. Secondary forms are classified by the specific type of material deposition (infiltration), storage, or replacement.

### Acquired amyloidosis

In primary (or AL) amyloidosis, the fibrillar protein is composed of  $\kappa$  and  $\lambda$  immunoglobulin light chains, produced by a proliferating clone of plasma cells [3]. These immunoglobulins can be found in urine as Bence-Jones proteins. A systemic disease that tends to follow a rapidly progressive course, primary amyloidosis is often seen in conjunction with plasma cell dyscrasia such as multiple myeloma or monoclonal gammopathies. Secondary (or AA) amyloidosis occurs in association with chronic inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis, and familial Mediterranean fever. Nephrotic syndrome and renal failure are common at presentation.

### Hereditary amyloidosis

Hereditary amyloidosis is the result of a mutation in one of a number of fibril precursor proteins, including transthyretin, apolipoprotein A-I or A-II, lysozyme, fibrinogen A $\alpha$  chain, gelsolin, and cystatin C. The phenotype varies according to the protein affected. Autosomal-dominant inheritance is typical.

### Cardiovascular involvement

Amyloidosis frequently affects the heart. The propensity for cardiovascular involvement is greatest in primary, senile, and certain hereditary forms of the disease. Cardiac disease is relatively less common in AA amyloidosis, but is a marker of unfavorable prognosis when present [4]. Amyloid fibrils may be deposited in the myocardium, papillary muscles, valves,

conduction system, and/or vessels, with consequent clinical manifestations.

### Clinical presentation of cardiac amyloidosis

Clinical suspicion of cardiac amyloidosis arises in the following circumstances: cardiac disease in the setting of established AL amyloidosis and/or plasma cell dyscrasia; ventricular dysfunction or arrhythmia and longstanding connective tissue disease or other chronic inflammatory disorder; any patient with restrictive cardiomyopathy of unknown etiology; left ventricular (LV) hypertrophy on echocardiography but a low-voltage electrocardiogram (ECG); and congestive heart failure of unknown origin refractory to standard medical therapy.

### Diagnosis of cardiac amyloidosis

The preliminary work-up for a patient with suspected cardiac amyloidosis includes a 12-lead ECG and two-dimensional echocardiography, with or without Holter monitoring [5]. A low-voltage ECG with increased septal and posterior LV wall thickness on echocardiography is specific for cardiac amyloidosis on non-invasive testing [5]. Other investigations that are of value include protein electrophoresis and genetic testing. A confirmatory biopsy (multiple specimens) is needed for diagnosis (*Figure 1*), since cardiac amyloidosis has no pathognomonic symptoms and signs, nor diagnostic findings. However, with advances in imaging, cardiovascular magnetic resonance (*Figure 2*) may prove to have value in diagnosis, treatment, and follow-up in cardiac amyloidosis [6].

### Management and outcome

Treatment is directed at both the underlying disease process and the cardiac complications. Systemic therapy is type-specific (i.e., chemotherapy), underscoring the importance of determining the precise etiology of amyloidosis [7]. Prognosis of AL amyloidosis is poor; however, in subgroups of patients, combined treatment with high-dose melphalan and autologous stem cell transplantation has resulted in hematological remission, improved five-year survival, and reversal of amyloid-related disease [5]. In contrast, senile systemic amyloidosis is characterized by slow progression not requiring alkylating agents [8]. Reactive AA amyloidosis may respond to anti-inflammatory and immunosuppressive drugs that reduce production of acute-phase reactant serum amyloid A protein. Ventricular dysfunction secondary to amyloidosis may be difficult to treat. Diuretics and

## Refresher corner

### Cardiac amyloidosis

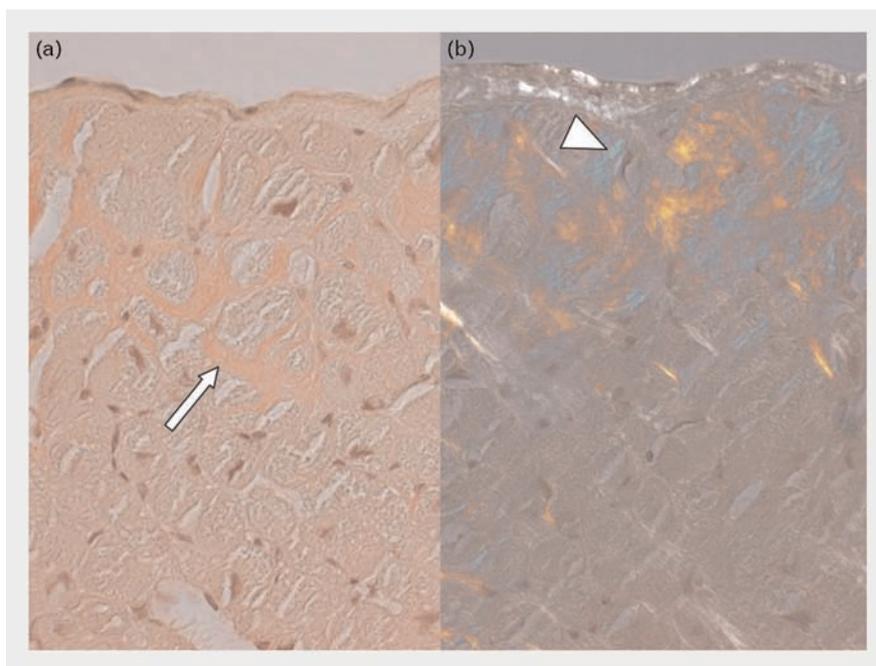


Figure 1. Subendocardial biopsy with Congo red-positive extracellular amorphous deposits (arrow, panel a), disrupting the organisation of the heart muscle. On the right (panel b) with optical double refraction, amyloid deposits partly with a characteristic blue color (arrowhead). Photograph provided by Waschkowski G, MD, Institute of Pathology, University of Bern.

vasodilators are used judiciously owing to the risk of hypotension with excessive falls in preload. Digoxin is contraindicated because it binds to amyloid fibrils and toxicity may develop at ordinary therapeutic doses. Complex ventricular arrhythmia has been documented in patients with cardiac amyloidosis and may be a predictor of sudden cardiac death. Beta blockers are administered with caution as they may promote atrio-

ventricular (AV) block and their negative inotropism is often poorly tolerated. Implantation of a permanent pacemaker is indicated in patients with symptomatic bradyarrhythmias or complete AV block. ■

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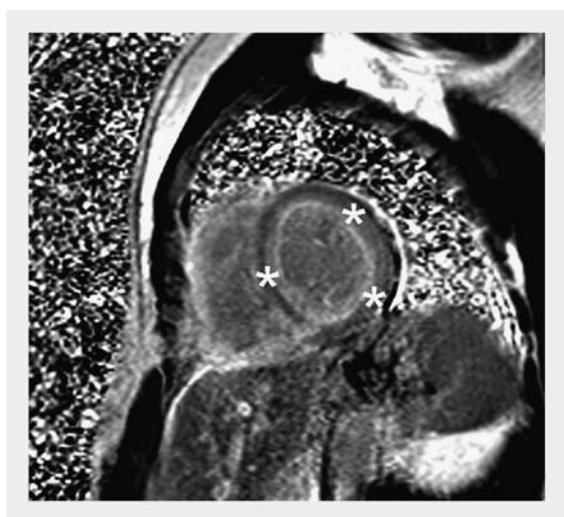


Figure 2. Short-axis view: diffuse, circumferential enhancement of the myocardium (asterisks) in late gadolinium CMR picture. Photograph provided by Wahl A, MD, Department of Cardiology, University of Bern.