Current Concepts of Cardiac Amyloidosis

Diagnosis, Clinical Management, and the Need for Collaboration

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KEYWORDS

• Cardiac amyloidosis • Multiple myeloma • TTR • Cardiotoxicity • Proteasome inhibitors • Immunomodulatory drugs

KEY POINTS

- Cardiac amyloidosis is a complex and vexing clinical condition that requires a high degree of suspicion for the diagnosis with a substantial amount of discipline to discern the extent of disease and the best available therapy.
- There is a complex interplay between multiple organ systems, and the clinical presentation may involve a myriad of confusing clinical symptoms.
- The diagnosis of cardiac amyloidosis can be confirmed with a combination of physical findings, cardiac biomarkers, noninvasive testing, and, if necessary, myocardial biopsy. Genetic testing is critical to establish the type of amyloidosis.
- The treatment of cardiac amyloidosis is determined by the type, either amyloid light-chain or transthyretin, or less likely, a very rare inherited amyloidosis.
- The future for drug development in the treatment of cardiac amyloidosis is bright, and the need for earlier diagnosis is imperative.

INTRODUCTION

Patients with cardiac amyloidosis commonly develop diastolic and systolic dysfunction, progressive heart failure (HF), arrhythmias, and symptoms of orthostatic hypotension. Amyloidosis is a rare group of diseases characterized by the extracellular deposition of misfolded precursor proteins in a beta-pleated sheet conformation that renders the proteinaceous material an insoluble fibril. Systemic deposition of these amyloid fibrils results in organ damage and dysfunction, with affected tissue demonstrating a characteristic apple-green birefringence under polarized light when stained with Congo red.[1] The nature of the organ dysfunction depends on the organ affected and the

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intensity of protein deposition. This review focuses on cardiac dysfunction but includes other organs and the manner in which that dysfunction may impact the cardiovascular system.

In order to have a solid basic understanding of cardiac amyloidosis, it is important to recognize that there are multiple sources of amyloid fibrils that can deposit in cardiac tissue. The 2 most common types of amyloidosis affecting the heart include light chain (AL) amyloidosis and transthyretin (TTR) amyloidosis (subcategorized into mutant [TTRm] and wild-type [TTRwt]), although other rarer systemic amyloid processes have been described that can affect the heart.[2] Given the tendency for amyloidosis to have systemic involvement, a diagnosis of cardiac amyloidosis should be strongly considered in patients presenting with HF who also have findings indicating other typical organ system dysfunction seen with systemic amyloidosis. Because protein deposition can be diffuse, the patterns of involvement can be myriad, and a clinician needs to be aware of the possible connections in order to detect the disease at the earliest possible moment. Commonly involved organ systems that may be affected by amyloidosis include the kidney, gastrointestinal tract, liver, pulmonary, soft tissue, and nervous system.

DIAGNOSIS

There are multiple classifications of the type of systemic amyloidosis that must be considered. The 2 most common, constituting more than 90% of all cardiac-related amyloidosis, are AL and TTR amyloidosis.

Amyloid Light-Chain Amyloidosis

AL amyloidosis is the most common systemic amyloidosis type in the United States with approximately 4500 new cases diagnosed yearly.[3] The disease is the result of an abnormal population of bone marrow plasma cells producing an improperly folded light chain protein (of either kappa or lambda type) that deposits systemically. It is mainly a disease of older individuals, frequently diagnosed in patients between ages 50 to 80, although cases have been reported at younger ages. Men are more commonly affected than women, representing approximately two-thirds of all cases.[3]

Cardiac involvement is estimated in more than 50% of patients diagnosed with AL amyloidosis and has been identified as the greatest predictor of poor prognosis.[4] Notably, AL amyloidosis is commonly associated with multiple myeloma, a plasma cell dyscrasia that frequently presents with hypercalcemia, renal insufficiency, anemia, and bony lytic lesions. Median life expectancy in patients with AL amyloidosis has been previously estimated to be approximately 1 year (0.75 years after HF onset), but this estimate has increased in recent years with the advent of new therapies and routine use of autologous hematopoietic stem cell transplantation in treatment.[4,5]

Transthyretin Amyloidosis

In TTR amyloidosis, the liver produces TTR (prealbumin), a protein that has an intrinsic potential and tendency to misfold and deposit in tissues, causing organ tissue damage and dysfunction. The generation and deposition of amyloid in this disease can be either the result of a TTRm or a gradual deposition of TTR protein over time that mimics a process of early aging, and an absence of a known transthyretin gene mutation, referred to as TTRwt. The most common TTRm gene mutations have been described to be a valine to isoleucine substitution at position 122 (Val122Ile), a valine to methionine substitution at position 30 (Val30Met), and threonine to alanine substitution at position 60 (Thr60Ala), although at least 34 mutations have been reported in the United States, and more than 100 worldwide.[6–8]

In general, in the United States, wild-type disease (TTRwt) is more commonly diagnosed in patients that are older and of African descent, whereas patients with a common mutation in TTR-m (Val122Ile) are more likely to be younger, white, and female.[6] Median survival for patients with either type of TTR amyloidosis is typically longer than patients with AL amyloidosis.[9,10]

SIGNS AND SYMPTOMS

Initial signs of cardiac amyloidosis can be subtle, with patients commonly noting symptoms of fatigue and weakness. As the disease advances, amyloid deposition throughout the heart frequently results in progressive mechanical cardiac dysfunction. The classic triad of HF symptoms (fatigue, shortness of breath, and edema) become evident and can raise suspicion for a diagnosis of cardiac amyloidosis (**Box 1**).

Amyloid deposition in the ventricles and atrium can result in biventricular wall thickening without dilation and subsequently increased atrial pressure, resulting in profound atrial dilation and atrial wall thickening.[11] These structural changes certainly are not detected until late in the process, and the development of important diastolic filling impairment will likely precede obvious structural changes. As the deposition persists, ultimately systolic left ventricular (LV) dysfunction ensues