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Light-chain cardiac amyloidosis

Anit K. Mankad, MD, FACC[a,*], Isata Sesay, MD[b], Keyur B. Shah, MD, FACC[b]

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ABSTRACT

Cardiac amyloidosis is an underrecognized condition, in which delays to diagnosis have great implications on management options, prognosis, and morbidity. Once cardiac tissue is infiltrated by amyloid fibrils, there is a cascade of pathologic changes that can display an array of clinical manifestations, from impaired relaxation of the ventricular myocardium to severe restrictive disease or even progressive systolic heart failure. Management is guided not only by recognizing the subtype of amyloidosis (primary, hereditary, and wild-type transthyretin amyloidosis), but also the clinical stage of the disease. It is important for those managing such patients to understand and differentiate disease associated with fibrils composed of transthyretin vs light-chain proteins. Kappa- and lambda-light chains of primary amyloidosis are particularly toxic to myocytes, leading to accelerated clinical illness in the face of intolerance to treatment and poor survival. Limitations to treatment of primary cardiac amyloidosis are related to multiorgan dysfunction and the inability to tolerate appropriate chemotherapy. Bortezomib, a selective protease inhibitor, has been shown to be and an effective and tolerable option for those with myocardial amyloid infiltration. Standard goal-directed optimal medical management for cardiomyopathy (such as beta-blockers and ace

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[a] *Division of Cardiology, Hunter Holmes McGuire Veterans Affairs Medical Center, Richmond, Virginia*
[b] *The Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia*
**Correspondence to: Anit K. Mankad, MD, Heart Failure/Transplantation, Division of Cardiology, McGuire Medical Center, 111-J, 1201 Broad Rock Blvd, Richmond, VA 23249.*
E-mail address: anit.mankad@va.gov (A.K. Mankad).

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inhibitors) does not offer a survival benefit with cardiac amyloidosis, and often is associated with adverse effects. Despite advances in treatment of advanced heart failure therapy, end-stage cardiomyopathy in the setting of amyloidosis is not well stabilized by inotropes or mechanical circulatory support, and offers restricted candidacy for heart transplantation. We review the salient features of cardiac amyloidosis to help general practitioners and subspecialists manage this unique clinical condition.

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Introduction

In 1886, Dr Carl Wild described a middle-aged woman with "weakness of the heart muscle." At autopsy, her ventricles were firm and resistant, and contained materials that stained with an iodine-sulfuric acid test.[1] This patient likely represented the first case of primary cardiac amyloidosis.

Amyloidosis is a relatively uncommon disease that requires a high index of clinical suspicion to make an early diagnosis. The disease is characterized by the extracellular deposition of insoluble fibrils made of misfolded protein. It constitutes a heterogeneous group of disorder with more than 31 structurally unrelated proteins that are known to cause amyloidosis.[2] This protein takes on apple-green birefringence under a polarized light microscope with Congo red staining.[1] The most important types of such fibrils that are known to infiltrate the heart are made up of immunoglobulin light chain and transthyretin (TTR), tetrameric transport protein for thyroxine and vitamin A that is produced by the liver.[3] Although considered similar in some regards, they are quite distinct with respect to clinical course, prognosis, and treatment. Primary (AL) amyloidosis is the most common and accounts for approximately 80% of all cases of clinically significant cardiac amyloidosis.[4] Transthyretin-derived amyloidosis accounts for 18% of all cases, and it is the second most common causes of cardiac amyloidosis.[4] Furthermore, wild-type TTR (ATTRwt) protein causes cardiac amyloidosis sporadically in the older population. Specifically, 25%-36% of the population older than 80 years of age are at risk to develop a slowly progressive, infiltrative amyloid cardiomyopathy secondary to ATTRwt.[5,6] In contrast, hereditary amyloidosis (ATTRm) is an autosomal dominant inherited disease associated with more than 100 point mutations in the TTR gene.[7] The mutant TTR protein has a tendency to affect the heart and nervous system. One of these variants worth mentioning is the Val22Ile, which is present in 3%-4% of Black Americans and carrying the mutation alone is associated with an increased risk of developing heart failure.[8]

The incidence of AL amyloidosis worldwide is 3-9 per million person-year.[9-11] Cardiac involvement is extremely common, ranging from 48%-90% of patients with AL amyloidosis.[4,12,13] Cardiac amyloidosis of this type has a slight male dominance (3:2 ratio) and a median age at diagnosis between 60 and 69 years.[10,11]

Presentation of cardiac amyloidosis

Cardiac amyloidosis can be more efficiently diagnosed if the practitioner maintains an index of suspicion in cases where an identifiable cause of the cardiomyopathy is not found. One of the setbacks is that diagnostic testing is often sent at a later stage of clinical illness, and there is a higher proportion of patients being diagnosed at an irreversible stage of illness. So, it is important to search for clues in the work-up that may lead to early assessment of amyloidosis.

As a systemic process, it becomes difficult to differentiate symptoms that point directly toward cardiac involvement. In particular, the typical patient with early amyloid disease may