

Isolated Cardiac Amyloidosis

Abstract

Isolated Cardiac amyloidosis is an obscure cause of heart failure. Although other causes of heart failure and other forms of amyloidosis have been recognized and discussed in detail, this entity is not frequently encountered. This case involves an 84 year old male who presented with fatigue, atrial fibrillation and a low ejection fraction. Further evaluation with cardiac biopsy resulted in the diagnosis of isolated cardiac amyloidosis; there was no sign of amyloid in the abdominal fat pad biopsy or other organs. We would like to focus this paper on isolated cardiac amyloidosis and its clinical significance.

Keywords: Amyloidosis; Creatinine; Dyslipidemia; Echocardiography; Hypertrophy

Case Report

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Abbreviations: EF: Ejection Fraction; AL : Light-Chain Amyloidosis; AA: Amyloid Amyloidosis; SAA: Serum Amyloid A Protein; ANP : Atrial Natriuretic Peptide

Case Presentation

An 84-year old African American male presents with increasing bilateral lower extremity edema as well as dyspnea on exertion and intermittent chest pain. His past medical history consists of hypertension, chronic back pain, benign prostate hypertrophy, dyslipidemia, atrial fibrillation, and chronic kidney disease with a baseline creatinine of about 1.6 mg/dl. Relevant medical history also included a hospitalization four years ago for chest pain and an abnormal stress test. The patient underwent a cardiac catheterization and was found to have stenosis of the left anterior descending artery of approximately 10% with a reduced ejection fraction (EF).

Physical exam showed orthostatic hypotension, bilateral crackles, atrial fibrillation with a capture rate of 75. Lab values revealed a B-type Natriuretic peptide elevation of 743 pg/ml and an elevated troponin of 0.45 ng/mL. A 12-lead electrocardiogram showed atrial fibrillation with a controlled ventricular response. Diagnostic testing included an echocardiography (echo) that indicated elevated right ventricular pressures, pulmonary arterial hypertension, concentric left and right ventricular hypertrophy and a thickened interatrial septum. He subsequently underwent a right and left cardiac catheterization that showed no valvular abnormalities or significant stenosis of the coronary arteries. However, he did have an elevated pulmonary artery mean systolic pressure of 35 mmHg and a right atrial pressure of 14 mmHg.

An infiltrative process was suspected and he underwent an abdominal pad biopsy that proved negative. Nevertheless, we had a high suspicion there was an infiltrative cardiomyopathy and performed an endomyocardial biopsy under fluoroscopy that was clinically significant for presence of amyloid: An apple green birefringence under polarized light when stained with Congo red. The negative fat pad biopsy and positive cardiac biopsy point towards an isolated cardiac amyloidosis case.

Since there is no definitive treatment for amyloidosis, we initiated treatment for heart failure with reduced ejection fraction and continue to treat any other symptoms the patient exhibits.

Discussion

Amyloidosis is defined as an accumulation of insoluble low molecular weight proteins in various organs like the heart, kidney, liver, and autonomic nervous system. Amyloidosis is classified based on the type of amyloid protein, the site of accumulation and whether it is systemic or localized. Amyloidosis is generally an under diagnosed disease due to the nonspecific presentation.

Systemic amyloidosis involves the viscera, blood vessels and connective tissue, whereas localized amyloidosis involves particular viscera. Cardiac amyloidosis may involve the myocardium, atria, ventricles, valves and small vessels of the heart. The most common types of cardiac amyloidosis include light-chain (primary) amyloidosis (AL) and familial. Less common types that involves the heart are: senile systemic amyloidosis (wild type TTR); secondary amyloidosis (amyloid amyloidosis or AA); and isolated atrial amyloidosis.

Light-chain amyloidosis (AL)

AL is seen in elderly persons over the age of 50 years. Though unusual, it can also occur as early as the third decade of life. AL is associated with B-cell lymphoproliferative disorders with the most commonly associated plasma cell dyscrasia being multiple myeloma. This type of protein is derived from clonal light chains and hence the name AL (light-chain amyloidosis).

In AL, the heart is involved in 50% of the cases. Cardiac enzyme elevation is generally seen from myocyte involvement secondary to cell necrosis. Symptomology includes chest discomfort with peripheral edema, and dyspnea. Hypertension is an unusual presentation; typically the blood pressure is normal or on the low side, and the patient may exhibit orthostatic hypotension secondary to cardiac involvement or autonomic neuropathy (18%). There may be a pleural effusion that can represent heart

failure or an amyloid pleural infiltrate. Patients may exhibit hepatic involvement from either right heart failure or direct infiltration. If there is hepatic infiltration, the liver is usually hard and non-tender during physical examination, as opposed to tender and firm in patients with right heart failure.

An EKG will show low voltage in the limb leads, but bundle branch blocks are rare. Concentric thickening of the ventricles and atrial septal infiltration is seen on echocardiography, and the granular, sparkling appearance of the myocardium with thickened heart valves are the primary factors that distinguish cardiac amyloidosis from hypertrophic cardiomyopathy. To differentiate amyloidosis from ischemic cardiomyopathy, many patients undergo cardiac catheterization, which typically shows normal coronary arteries.

Cardiac MRI is beneficial and non-invasive, thus far it is not helpful in determining a definitive diagnosis because the sensitivity is not known and the specificity can be low. A tissue biopsy is another diagnostic tool, with the most common site being an abdominal fat pad biopsy, yet it is positive in only 70% of the cases. Cardiac biopsy is the definitive diagnostic test with a 100% sensitivity and it is a relatively safe and simple procedure. It is reasonable to obtain a bone marrow biopsy and look for multiple myeloma or other less common disorders of the bone marrow, which are both valuable in guiding therapy.

Hereditary or familial amyloidosis

Familial (hereditary systemic amyloid) is usually inherited as an autosomal dominant trait. The majority of this amyloid is associated with a gene mutation in the plasma protein transthyretin, a protein synthesized predominantly in the liver, and also in small amounts in the choroid plexus. There are more than 75 different types of point mutations described in the literature that are responsible for this disease. The two primary mutations isolated are: methionine for valine; and isoleucine for valine. The latter is worth mentioning because 4% of African American males are heterozygous for this mutation and can present with cardiomyopathy in the 5th or 6th decade of life. The most common clinical presentation is neurological involvement. Although the transthyretin protein is produced in the liver, it usually does not cause any liver damage.

The Echocardiogram findings are similar to AL, but the survival rate is much higher. Unlike AL, the abdominal fat biopsy is almost always negative, and therefore, an endo-myocardial biopsy is required for diagnosis. Apart from symptomatic management, the definitive treatment option is liver transplantation to inhibit the synthesis of mutated transthyretin; genetic testing prior to the procedure is essential in order to confirm the mutation. Depending on the degree of cardiac involvement, heart transplantation should be considered as well.

Senile systemic amyloidosis

The type of protein involved in diagnosing senile systemic amyloidosis is a wild type transthyretin protein (wild type TTR protein). It is called wild type because it is a natural form of the protein without any mutation. It usually affects men above the age of 60. As the name suggests, it is a systemic disease involving the GI tract, the liver, bone marrow, the tongue, and so forth, yet it

is most commonly confined to the heart. Infrequently, there is a presentation of carpal tunnel syndrome.

The diagnosis is usually made by endomyocardial biopsy, but there should also be echocardiography findings suggestive of amyloidosis. It is not uncommon to have sparse deposit of wild type TTR protein in the myocardium in elderly men. Other types of amyloidosis like AL and mutant transthyretin protein should be looked for prior to starting treatment. The median survival rate of heart failure secondary to wild type TTR is 7.5 years, which is much better compared to the mean survival rate of AL, which is only 13 months.

Secondary systemic amyloidosis (amyloid amyloidosis or AA)

This is previously known as secondary amyloidosis. It is associated with and secondary to chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, TB, etc. With advances in medicine and our increased ability to control inflammation, this is a more and more uncommon condition. The type of protein involved is serum amyloid A protein (SAA) which is seen during an inflammatory condition and is an acute phase reactant. The most commonly involved organs are the kidneys and the liver; the heart is generally not involved. The course of treatment is usually focused on the underlying disease process itself.

Isolated atrial amyloid

The type of protein seen in this variant is an atrial Natriuretic peptide (ANP). It only affects the atria, is not a systemic disease, is more common in females, and is usually diagnosed incidentally at the time of autopsies. As it only involves the atria and spares the rest of myocardium, heart failure is unlikely, but it can cause atrial conduction defects in the elderly (Figure 1).



Figure 1: Horizontal cross section of the heart. The heart is hypertrophic and the light-colored masses observed in the ventricular wall are amyloid deposits.

Conclusion

Cardiac amyloidosis involves deposition of misfolded proteins, mainly in the myocardium and is less frequently observed in the

atria, pericardium, endocardium, and vasculature. Around 50% of patients have AL type, whereas only 5% constitute AA. Cardiac involvement manifests as congestive heart failure, arrhythmias, microvascular involvement (resulting in tissue ischemia and infarction), and restrictive pattern (with myocardium deposition).

Patients with unexplained heart failure and thickened cardiac walls, non-dilated ventricular cavity on echocardiogram and low voltage complexes on EKG have a high clinical suspicion of an infiltrative disease such as amyloidosis. Echocardiogram and magnetic resonance imaging are not definitive diagnostic tests. Tissue analysis is essential to confirm cardiac amyloidosis. Even though definitive diagnosis is made by tissue biopsy the treatment can vary depending on different types. Further work up to determine the type is required for guiding therapy.

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